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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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R C van Dijk

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Bisarylurea derivatives

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Bisarylurea derivatives

Bisarylurea derivatives

The present invention relates to bisarylurea derivatives, bisarylurea derivatives as medicaments, bisarylurea derivatives as inhibitors of raf-kinase, the use of bisarylurea derivatives for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said bisarylurea derivatives, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the $p21^{ras}$/raf pathway.

The $p21^{ras}$ gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

The $p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). Oncogenic Ras mutations have been identified for example in lung cancer, colorectal cancer, pancreas, thyroid cancer, melanoma, bladder tumours, liver tumour, kidney tumor, dermatological tumours and haematological tumors (Ddjei et al. (2001), J. Natl. Cancer Inst.

93(14), 1062-74; Midgley, R.S. and Kerr, D.J. (2002) Critical Rev. Onc/ hematol 44, 109-120; Downward, J. (2003), Nature reviews 3, 11-22). In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by growth factor receptors in almost all tissues (Avruch et al. (1994) Trends Biochem. Sci., 19, 279-83).

Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras endogenous GTPase activity and other regulatory proteins. The ras gene product binds to guanine triphosphate (GTP) and guanine diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of Ras that is active. In the ras mutants in cancer cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants (Magnuson et al. (1994) Semin. Cancer Biol., 5, 247-53). The ras proto-oncogene requires a functionally intact c-raf1 proto-oncogene in order to transduce growth and differentiation signals initiated by receptor and non-receptor tyrosine kinases in higher eukaryotes.

Activated Ras is necessary for the activation of the c-raf-1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein (Ser/Thr) kinase are now well characterized . It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK also called ERK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype see: Daum et al. (1994) Trends Biochem. Sci., 19, 474-80; Fridman et al. (1994) J Biol. Chem., 269, 30105-8. Kolch et al. (1991) Nature, 349, 426-28) and for review Weinstein-Oppenheimer et al. Pharm. & Therap. (2000), 88, 229-279.

Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75; Geiger et al. (1997), Clin. Cancer Res. 3(7): 1179-85; Lau et al. (2002), Antisense Nucl. Acid. Drug Dev. 12(1): 11-20 ; McPhillips et al. (2001), Br. J. Cancer 85(11): 1753-8).

Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in The oncogene handbook; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184; Rapp, U.R., et al. (1990) Inv Curr. Top. Microbiol. Amunol. Potter and Melchers (eds), Berlin, Springer-Verlag 166:129-139).

Three isozymes have been characterized:

c-Raf (also named Raf-1, c-raf-1 or c-raf1) (Bonner, T.I., et al. (1986) Nucleic Acids Res. 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) Nucleic Acids Res. 15:595-609), and B-Raf (Qkawa, S., et al. (1998) Mol. Cell. Biol. 8:2651-2654; Sithanandam, G. et a. (1990) Oncogene:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) Oncogene 5:345-351).

Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) Mol. Cell. Biol. 10:2503-2512; Rapp, U.R., et al. (1987) in Oncogenes and cancer S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific

Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with Escherichia coli expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in Oncogenes and cancer; S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) Mol. Cell. Biol. 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers e.g. colon, ovarien, melanomas and sarcomas (Davies, H., et al. (2002), Nature 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E), leading to constitutive kinase activity and transformation of NIH3T3 cells.

Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase in a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in The Oncogene Handbook, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) Nature (London) 320:540-543).

c-Raf function is required for transformation by a variety of membrane-bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) Nature (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation (Morrison, D.K., et al. (1989) Cell 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), colony-stimulating factor (Baccarini, M., et al. (1990) EMBO J. 9:3649-3657), insulin

(Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Habor Sym. Quant. Biol. 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in Genes and signal transduction in multistage carcinogenesis, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf oncogenes activate transcription from Ap-I/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) Science 344:463-466; Kaibuchi, K., et al (1989) J. Biol. Chem. 264:20855-20858; Wasylyk, C., et al. (1989) Mol. Cell. Biol. 9:2247-2250).

There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by autophosphorylation or may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased vascular permeability; (iii) subsequent dissolution of the basement membrane and extravisation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

Normal angiogensesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends in Pharmacol Sci. 16:54 66; Shawver et al, DOT Vol. 2, No. 2 February 1997; Folkmann, 1995, Nature Medicine 1:27-31.

In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkmann, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.) Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF or basic fibroblast growth factor bFGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through

the Ras/Raf/Mek/Erk kinase cascade and protects endothelial cells from apoptosis (Alavi et al. (2003), Science 301, 94-96; Hood, J.D. et al. (2002), Science 296, 2404; Mikula, M. et al. (2001), EMBO J. 20, 1952; Hauser, M. et al. (2001), EMBO J. 20, 1940; Wojnowski et al. (1997), Nature Genet. 16, 293). Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page 293- 296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

For the identification of a signal transduction pathway and the detection of cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examintion of particular steps in the signal transduction cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the examination of kinase dependent signal transduction

pathways in animal and/or cell culture models or any of the clinical disorders listed throughout this application.

The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 J. Biol. Chem. 267, Page 14535).

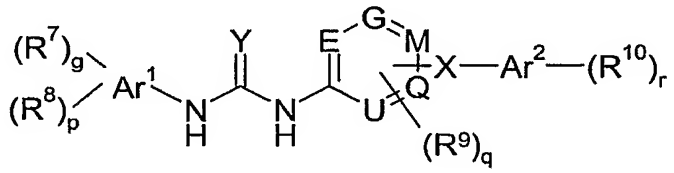
For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., Nature Drug Discovery 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., J. of. Biomolecular Screening, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with γATP can be measured. In the presence of an inhibitory compound no signal or a decreased radioactive signal is detectable. Furthermore homogeneous time-resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods (for example Sills et al., J. of Biomolecular Screening, 2002, 191-214).

Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for exaple Ross et al., Biochem. J., 2002, 366, 977-981).

The present invention provides compounds generally described as bisarylurea derivatives, including both aryl and/or heteroaryl derivatives which are preferably kinase inhibitors and more preferably inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the

inhibitors preferably are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds preferably are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compound of Formula I or a pharmaceutically acceptable salt thereof can be administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, preferably solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds preferably are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus type1) induced immunodeficiency (Popik et al. (1998)J Virol, 72: 6406-6413) and infection disease, Influenza A virus (Pleschka, S. et al. (2001), Nat. Cell. Biol, 3(3):301-5) and Helicobacter pylori infection (Wessler, S. et al. (2002), FASEB J., 16(3): 417-9).

Therefore, subject of the present invention are bisarylurea derivatives of formula I



I

wherein

Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

E, G, M, Q and U are selected, independently from one another, from carbon atoms and nitrogen atoms, with the proviso that one or more of E, G, M, Q and U are carbon atoms and that X is bonded to a carbon atom,

R^7 is independently selected from a group consisting of Het, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nNR^{12}(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $O(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kOR^{12}$, $(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$ and $NR^{12}(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, wherein

R^5, R^6 are in each case independently from one another selected from H and A;

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal,

$CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, $CH_2CH=N$-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S; whereby said heterocyclic residue optionally is substituted by one or more substituent, selected from A, R^{13}, =O, =S and $=N-R^{14}$,

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het is a saturated, unsaturated or aromatic heterocyclic residue which preferably contains 1 to 3 heteroatoms, more preferably 1 or 2 heteroatoms, the heteroatoms beeing preferably selected from N, O and S, more preferably from N and O; whereby said heterocyclic residue is optionally substituted by one ore more substituents, selected from a group consisting of A, R^{13}, =O, =S, =N-R^{14}, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein

Ar^6	is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,
k, n and m	are independently of one another 0, 1, 2, 3, 4, or 5,
X	represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein
Q	is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, (O-$CHR^{18})_j$, $(CHR^{18}$-$O)_j$, CR^{18}=CR^{19}, (O-$CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}$-$O)_j$, C=O, C=S, C=NR^{15}, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, C(=O)N(R^{15}), N(R^{15})C(=O), OC(=O)N(R^{15}), N(R^{15})C(=O)O, CH=N-O, CH=N-NR^{15}, OC(O)NR^{15}, NR^{15}C(O)O, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein
h, i	are independently from each other 0, 1, 2, 3, 4, 5, or 6, and
j	is 1, 2, 3, 4, 5, or 6,
Y	is selected from O, S, NR^{21}, C(R^{22})-NO_2, C(R^{22})-CN and $C(CN)_2$, wherein
R^{21}	is independently selected from the meanings given for R^{13}, R^{14} and
R^{22}	is independently selected from the meanings given for R^{11}, R^{12},

	g	is 1, 2 or 3, preferably 1 or 2,
	p, r	are independently from one another 0, 1, 2, 3, 4 or 5,
	q	is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
	u	is 0, 1, 2 or 3, preferably 0, 1 or 2,
	and	
	Hal	is independently selected from a group consisting of F, Cl, Br and I;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C_1-C_6

alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the term "C_1-C_6 alkyl" preferably refers to an alkyl group as defined abovecontaining at least 1, and at most 6, carbon atoms. Examples of branched or straight chained "C_1-C_6 alkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, t-butyl, n-pentyl and isopentyl.

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

As used herein, the term "C_1-C_6 alkylene" preferably refers to an alkylene group, as defined above, which contains at least 1, and at most 6, carbon atoms respectively. Examples of "C_1-C_6 alkylene" groups useful in the present invention include, but are not limited to, methylene, ethylene and n-Propylene.

As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

As used herein, the term "C_1-C_6 haloalkyl" preferably refers to an alkyl group as defined above containing at least 1, and at most 6, carbon atoms substituted with at least one halogen, halogen being as defined herein. Examples of branched or straight chained "C_1-C_6 haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

As used herein, the term "cycloalkyl" or "C_3-C_7 cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms and which optionally includes a C_1-C_6 alkyl linker through which it may be attached. The C_1-C_6 alkyl group is as defined above. Exemplary "C_3-C_7 cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, which are preferably selected from the cycloalkyl-groups as defined above, wherein one or two carbon atoms are replaced by hetero atoms, selected from the group consisting of O, N and S, which optionally is substituted by one or more substituents, preferably selected from alkyl, =O, =S and substituted or unsubstituted imino groups.

As used herein, the term "C_3-C_7 cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical having from three to seven carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-

diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl" preferably refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO_2, O or N, optionally substituted with substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 haloalkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C_1-C_6 perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO_2, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or napthalene ring systems. Exemplary optional substituents include C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C_1-C_6 perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a C_1-C_6 alkyl linker, wherein C_1-C_6 alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to, benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These hetroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulfanyl, C_1-C_6 haloalkylsulfanyl, C_1-C_6 alkylsulfenyl, C_1-C_6 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, C_1-C_6 perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five - to seven -membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more

heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" preferably refers to the group R_aO-, where R_a is alkyl as defined above and the term "C_1-C_6 alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C_1-C_6 alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy.

As used herein, the term "haloalkoxy" preferably refers to the group R_aO-, where R_a is haloalkyl as defined above and the term "C_1-C_6 haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the haloalkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary C_1-C_6 haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

As used herein the term "aralkoxy" preferably refers to the group R_CR_BO-, where R_B is alkyl and R_C is aryl as defined above.

As used herein the term "aryloxy" preferably refers to the group R_CO-, where R_C is aryl as defined above.

As used herein, the term "alkylsulfanyl" preferably refers to the group R_AS-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "haloalkylsulfanyl" preferably refers to the group R_DS-, where R_D is haloalkyl as defined above and the term "C_1-C_6 haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "alkylsulfenyl" preferably refers to the group $R_AS(O)$-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "alkylsulfonyl" preferably refers to the group R_ASO_2-, where R_A is alkyl as defined above and the term "C_1-C_6 alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

As used herein, the term "oxo" preferably refers to the group =O.

As used herein, the term "mercapto" preferably refers to the group –SH.

As used herein, the term "carboxy" preferably refers to the group –COOH.

As used herein, the term "cyano" preferably refers to the group –CN.

As used herein, the term "cyanoalkyl" preferably refers to the group $-R_BCN$, wherein R_B is alkylen as defined above. Exemplary "cyanoalkyl" groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

As used herein, the term "aminosulfonyl" preferably refers to the group –SO_2NH_2.

As used herein, the term "carbamoyl" preferably refers to the group –C(O)NH_2.

As used herein, the term "sulfanyl" shall refer to the group –S-.

As used herein, the term "sulfenyl" shall refer to the group –S(O)-.

As used herein, the term "sulfonyl" shall refer to the group –$S(O)_2$- or -SO_2-.

As used herein, the term "acyl" preferably refers to the group R_FC(O)-, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

As used herein, the term "aroyl" preferably refers to the group R_CC(O)-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group R_EC(O)-, where R_E is heteroaryl as defined herein.

As used herein, the term "alkoxycarbonyl" preferably refers to the group R_AOC(O)-, where R_A is alkyl as defined herein.

As used herein, the term "acyloxy" preferably refers to the group R_FC(O)O-, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroyloxy" preferably refers to the group R_CC(O)O-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyloxy" preferably refers to the group R_EC(O)O-, where R_E is heteroaryl as defined herein.

As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group C=O.

As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group C=S.

As used herein, the term "amino", "amino group" or "imino moiety" preferably refers to the group $NR_GR_{G'}$, wherein R_G and $R_{G'}$, are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both R_G and $R_{G'}$ are hydrogen, $NR_GR_{G'}$ is also referred to as "unsubstituted amino moiety" or "unsubstituted amino group". If R_G and/or $R_{G'}$ are other than hydrogen, $NR_GR_{G'}$ is also referred to as "substituted amino moiety" or "substituted amino group".

As used herein, the term "imino" or "imino moiety" preferably refers to the group $C=NR_G$, wherein R_G is preferably selected from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If R_G is hydrogen, $C=NR_G$ is also referred to as "unsubstituted imino moiety". If R_G is a residue other than hydrogen, $C=NR_G$ is also referred to as "substituted imino moiety".

As used herein, the term "ethene-1,1-diyl moiety" preferably refers to the group $C=CR_KR_L$, wherein R_K and R_L are preferably selected, independently from one another, from the group consisting of hydrogen, halogen, alkyl, haloalkyl, alkenyl, cycloalkyl, nitro, alkylenecycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both hydrogen R_K and R_L are hydrogen, $C=CR_KR_L$ is also referred to as "unsubstituted ethene-1,1-diyl moiety". If one of R_K and R_L or both are a residue other than hydrogen, $C=CR_KR_L$ is also referred to as "substituted ethene-1,1-diyl moiety".

As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more

stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulae I above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral Centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formulae I are included within the scope of the compounds of formulae I and preferably the formulae and subformulae corresponding thereto.

Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids, such as β-camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); an example of a suitable eluent is a hexane/isopropanol/ acetonitrile mixture.

The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

It is of course also possible to obtain optically active compounds of the formula I by the methods described above by using starting materials which are already optically active.

Unless indicated otherwise, it is to be understood that reference to compounds of formula I preferably includes the reference to the compounds of formula I' and I''. Unless indicated otherwise, it is to be understood that reference to the compounds of formula I, I' and I'' preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae I.1 to I.20 and preferably formulae Ia to Iw. It is also understood that the following embodiments, including uses and compositions, although recited with respect to formula I are preferably also applicable to formulae I', I'' and sub formulae I.1 to I.20 and preferably formulae Ia to Iw.

Even more preferred are compounds of formula I

wherein

Ar^1, Ar^2	are selected independently from one another from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,
R^7	is independently selected from a group consisting of Het, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$,

		$NR^{11}(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nNR^{12}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kOR^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$ and $NR^{12}(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, wherein
	R^5, R^6	are in each case independently from one another selected from H and A, and
	n and/or k	independently are 0, 1, 2, 3 or 4, preferably 1, 2, 3 or 4, and even more preferred is 2 or 3;
	R^8, R^9 and R^{10}	are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$, wherein

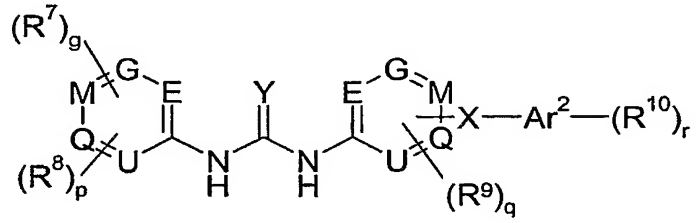
n and/or k	independently are 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3, and even more preferred are 0 or 2;
X	represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein
Q	is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}\text{-}O)_j$, C=O, C=$NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, $CH=N\text{-}NR^{15}$, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein
h, i	are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3 and
j	is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,
g	is 1 or 2, preferably 1,
p	is 1, 2 or 3, preferably 1 or 2, and
r	is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are especially compounds of formula I in which one or more substituents or groups, preferably the major part of the substituents or groups has a meaning which is indicated as preferred, more preferred, even more preferred or especially preferred.

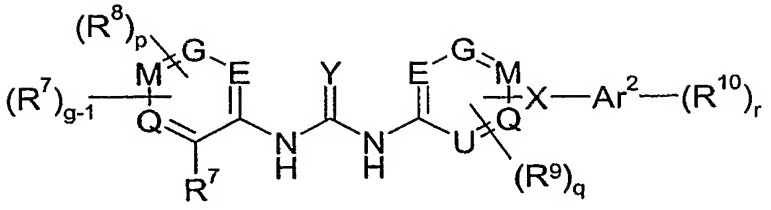
In compounds of formula I, E, G, M, Q and U constitute, together with the carbon atom that E and U are bound to, a bivalent 6-membered aromatic or nitrogen containing heteroaromatic ring. Preferably, one or more of E, G, M, Q and U, more preferably two or more of E, G, M, Q and U and especially three or more of E, G, M, Q and U are carbon atoms. Especially preferred, none or one of E, G, M, Q and U is a nitrogen atom. Especially preferred, E, G, M, Q and U constitute, together with the carbon atom that E and U are bound to, a 6-membered aromatic or nitrogen containing heteroaromatic ring, selected from the group consisting of phenylen, pyridinylen and pyrimydylen, wherein X is preferably bonded to a carbon atom. The substituents R^9 are preferably bound to a carbon atom.

More preferred as compounds of formula I are compounds of formula I',



(I')

wherein each of E, G, M, Q and U is independently from one another selected from carbon atoms and nitrogen atoms, with the proviso that in each of the E, G, M, Q and U containing 6-membered rings, one or more of E, G, M, Q and U are carbon atoms, and the further proviso that X and preferably substituents $(R^7)_g$ and $(R^8)_p$ are bonded to a carbon atom, respectively. More preferably, in the E, G, M, Q and U containing 6-membered ring one or more times substituted by R^7, U is CR^7, where R^7 is as defined above/below. Accordingly, especially preferred as compounds of formula I and compounds of formula I' are compounds of formula I'',



(I'')

wherein each residue R^7 is independently selected from the meanings given above/below.

In compounds of formula I, the term alkyl preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a branched alkyl residue comprising 3, 4, 5, 6, 7, 8 ,9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number of carbon atoms of the alkyl residue. For example, a methyl group can comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula I, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro

methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-nentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isoproply and tert.-butyl.

In compounds of formula I, alkenyl is preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

In compounds of formula I, alkylene is preferably unbranched and is more preferably methylene or ethylene, furthermore preferably propylene or butylene.

In compounds of formula I, alkylenecycloalkyl preferably has 5 to 10 carbon atoms and is preferably methylenecyclopropyl, methylenencyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenencycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.

In compounds of formula I, the term "alkoxy" preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above. More preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives are selected from the group consisting of O-CCl_3, O-CF_3, O-C_2Cl_5, O-C_2F_5, O-$C(CCl_3)_3$ and O-$C(CF_3)_3$.

In compounds of formula I, the term "alkoxyalkyl" preferably comprises branched and unbranched residues, more preferred unbranched residues, of formula C_uH_{2u+1}-O-$(CH_2)_v$, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v 1 to 4.

In compounds of formula I the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

In compounds of formula I, cycloalkyl preferably has 3 – 7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl. The term "cycloalkyl", as used herein preferably also includes saturated heterocyclic groups, wherein one or two carbon atoms are substituted by hetero atoms, selected from the group consisting of O, NH, NA and S, wherein A is as defined as above/below. Cycloalkyl residues as defined herein can optionally be substituted, the substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal.

In compounds of formula I, Ar^3 to Ar^6 are preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$.

In compounds of formula I, Het is preferably an optionally substituted aromatic heterocyclic residue and even more preferred and optionally substituted saturated heterocyclic residue. In substituted saturated heterocyclic residues, the substituents are preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. Even more preferred, Het is selected from the group consisting of 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-

hydroxyethy))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, chinolinyl, isochinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl. Further preferred, Het as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. More preferred, Het is either unsubstituted or substituted once or twice by =O.

In compounds of formula I, saturated heterocyclyl is preferably a substituted or unsubstituted saturated heterocyclic residue, more preferred an unsubstituted saturated heterocyclic residue, preferably selected from the saturated groups given above in the definition of Het. Further preferred, saturated heterocyclyl as defined above is optionally substituted by one or more substituents preferably selected from A, R^{13}, =O, =S, =N-R^{14}, CN and hal. More preferred, saturated heterocyclyl is either unsubstituted or substituted once or twice by =O.

In compounds of formula I, aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S, are preferably selected from the definitions given herein for aryl, heteroaryl and/or Het. Heteroaryl is more preferably furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl and even more preferably pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and/or imidazolyl. Aryl more preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene

rings to form, for example, anthracene, phenanthrene, or napthalene ring systems. Even more preferably, aryl is selected from the group consisting of phenyl, 2-naphthyl, 1-naphthyl, biphenyl.

In compounds of formula I, Ar^1 is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, and especially from phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl and oxazolyl. Especially preferred, Ar^1 is phenyl or pyridinyl.

In compounds of formula I, Ar^2 is preferably selected from the group consisting of phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl and imidazolyl, even more preferably from phenyl, pyridinyl and pyrimidyl and especially preferred from phenyl and pyridinyl.

If $R^5$and/or R^6 is A, then A is preferably selected, independently from one another in each case, from the group consisting of alkyl, cycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, more preferably preferably from the group consisting of alkyl, cycloalkyl, alkoxy and alkoxyalkyl, and especially is alkyl.

Preferably, the sum of h and i in one residue exceeds 0.

Preferably, the sum of n and k in one residue exceeds 0.

In R^7, n and/or k are preferably not 0.

In R^7, $(CR^5R^6)_n$ and/or $(CR^5R^6)_k$ is preferably linear or branched alkylen, preferably linear or branched C_1-C_4 alkylen, which is optionally substituted as described above/below and preferably is unsubstituted.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R^8, R^9 and/or R^{10} and especially in R^{10}.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein in the residues R^7, n is 1, 2 or 3 and especially is 2.

Another preferred aspect of the instant invention relates to compounds of formula I, wherein X represents a bridging group, selected from $(CR^{11}R^{12})_h$ or $(CHR^{11})_h$-Q-$(CHR^{12})_i$.

The invention relates in particular to compounds of the formula I in which at least one of said radicals has one of the preferred meanings given above.

Some more preferred groups of compounds may be expressed by the following sub-formulae I.1) to I.20), which correspond to the formula I and in which radicals not denoted in greater detail are as defined in the formula I, but in which

I.1) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl;

I.2) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl, and

p is 1, 2 or 3;

I.3) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3, and

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$;

I.4) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms,

Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$;

I.5) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1;

I.6) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl,

benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1, and

u is 0;

I.7) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$,

$(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S;

I.8) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,.

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl;

I.9) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$;

I.10) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl,

benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$,

$(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1;

I.11) Ar^1 is phenyl, pyridinyl, pyrimidyl, chinolinyl, isochinolinyl, thiophenyl, thiadiazolyl, benzothiadiazolyl, oxazolyl, isoxazolyl, pyrazolyl or imidazolyl, preferably phenyl, pyridinyl, chinolinyl, isochinolinyl, thiophenyl, benzothiadiazolyl, oxazolyl, isoxazolyl or oxazolyl, even more preferably phenyl or pyridinyl,

p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.12) p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4

carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.13) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

n is 0 or 1,

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$,

$(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.14) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

u is 0, and

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.15) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, wherein

q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2,

CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.16) q is 0 or 1, and

X is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,

Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

		R^{10}	is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein
		n	is 0, 1 or 2, preferably 0 or 1 and
		r	is 0, 1 or 2, preferably 0 or 1;
	I.17)	X	is selected from the group consisting of O, S, NR^{11}, $CHOR^{11}$, CH_2, CH_2CH_2, OCH_2, CH_2O, OCH_2CH_2, CH_2CH_2O, preferably O, S and CH_2 and especially O and S,
		Ar^2	is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and
		R^{10}	is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$,

$(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.18) Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl; and

R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.19) R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4

carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,

n is 0, 1 or 2, preferably 0 or 1 and

r is 0, 1 or 2, preferably 0 or 1;

I.20) R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, and

r is 0, 1 or 2, preferably 0 or 1.

One preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein p

is 1, 2 or 3 and R^8 is independently selected from the group consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF_3, $C(CF_3)_3$, SO_2CF_3, methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy ($OC(CF_3)_3$), methyl sulfanyl (SCH_3), ethyl sulfanyl (SCH_2CH_3), acetyl ($COCH_3$), propionyl ($COCH_2CH_3$), butyryl ($COCH_2CH_2CH_3$). If p is 2 or 3, all substituents can be the same or different.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is selected from the group consisting of S, N-R^{21}, CH_2, CH_2CH_2, OCH_2 and CH_2O.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is selected from the group consisting of S, CH_2.

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is O.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of $C(R^{22})$-NO_2, $C(R^{22})$-CN and $C(CN)_2$.

Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of O, S and NR^{21}.

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is selected from the group consisting of O and S.

Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Y is O.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^2 is pyridinyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein r is either 0 or 1. If r is 1, R^{10} is preferably $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$, wherein n in 0. In this embodiment, R^{11} is preferably selected from the group consisting of H and A and more preferred from H and alkyl, and R^{12} is preferably selected from the group consisting of H and A and more preferred from H and alkyl. Especially preferred as residue R^{10} are carbamoyl, more preferred alkyl carbamoyl or dialkyl carbamoyl, even more preferred methyl carbamoyl or dimethyl carbamoyl, ethyl carbamoyl or diethyl carbamoyl and especially preferred methyl carbamoyl (-$CONHCH_3$). This embodiment is especially preferred when Ar^2 is pyridinyl. When Ar^2 is pyridinyl, R^{10} is preferably bonded in a vicinal position to the nitrogen atom of the pyrindiyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 is phenyl.

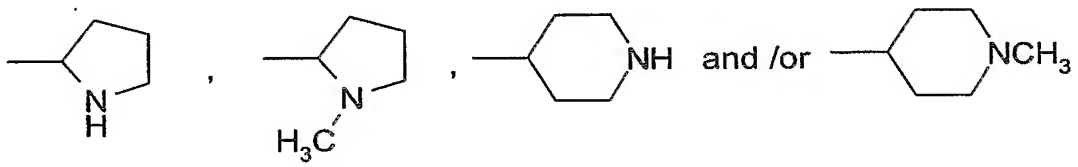
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein R^7 is independently selected from a group consisting of Het, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$,

$O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, and more preferably from OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, , and even more preferably $O(CH_2)_kR^{13}$, $NR^{11}(CH_2)_kR^{13}$, $O(CH_2)_kOR^{13}$, $NR^{11}(CH_2)_kOR^{13}$, $O(CH_2)_kNR^{11}R^{12}$, $NR^{11}(CH_2)_kNR^{11}R^{12}$. In this embodiment, k is preferably 1, 2 or 3

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein R^7 comprises a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7- membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, which optionally is substituted by one or more substituent, selected from A, R^{13}, =O, =S and =N-R^{14}. In this embodiment, the heterocyclus is preferably selected from morpholine, piperazine, piperidne, pyrrolidine, especially from 1-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 1-(4-(2-hydroxyethy))-piperazyl, 4-morpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, and/or oxomorpholine, oxopiperazine, oxopiperidine and oxopyrrolidine. More preferably, the oxo substituted heterocyclus is selected from 2-oxo-piperidin-1-yl, 2-oxo-piperidin-4-yl, 1-methyl-2-oxo-piperidin-4-yl, 2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl, 4-methyl-2-oxo-piperazin-1-yl amine, 4-(2-hydroxyethy)-2-oxo-piperazin-1-yl, 3-oxo-morpholin-4-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-pyrrolidin-5-yl and/or 3-oxo-piperidin-1-yl, 3-oxo-piperidin-4-yl, 1-methyl-3-oxo-piperidin-4-yl, 3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl, 4-methyl-3-oxo-piperazin-1-yl amine, 4-(2-hydroxyethy)-3-oxo-piperazin-1-yl, 2-oxo-morpholin-4-yl, 3-oxo-pyrrolidin-1-yl, 4-oxo-pyrrolidin-3-yl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein R^7 comprises a terminal group R^{11}, R^{12}, R^{13} or R^{14}, preferably a group R^{13}, that is selected from cycloalkyl and Het, more preferred from cycloalkyl and

saturated heterocyclyl and especially from saturated heterocyclyl. In this embodiment, saturated heterocycl is preferably selected from 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-methyl-piperidin-4-yl, 1-methyl-piperidin-3-yl, 1-methyl-piperidin-2-yl, 2-piperazyl, 3-piperazyl, 2-(4-methyl)-piperazyl, 3-(4-methyl)-piperazyl, 4-methylpiperazin-2-yl amine, 4-methylpiperazin-3-yl amine, 2-(4-(2-hydroxyethy))-piperazyl, 3-(4-(2-hydroxyethy))-piperazyl, 3-morpholinyl, 2-morpholinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, and and especially from



Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or more, preferably one substituent R^7 that is selected from the group consisting of $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, wherein R^{11}, R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 1, 2 or 3 and especially is 1 or 2, and k is is as defined above, preferably k is 1 to 4 and preferably 1, 2 or 3. In this embodiment R^{11}, R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this embodiment, one or two substituents R^7 and preferably one substituent R^7 that is especially preferably selected from the group consisting of $NHCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $NHCH_2C(CH_3)NH_2$, $OCH_2C(CH_3)NH_2$, $NHC(CH_3)CH_2NH_2$, $OC(CH_3)CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$ and $N(CH_3)CH_2CH_2OCH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein

q is 0, i.e. the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety is unsubstituted.

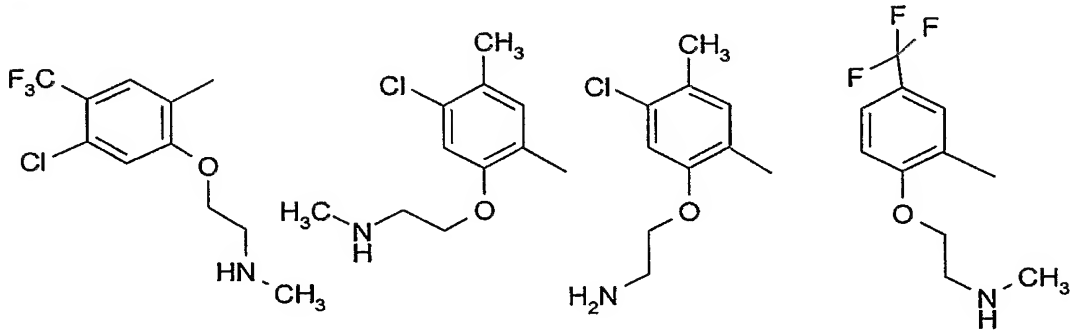
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein q is 1, i.e. the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety is substituted by one substituent, preferably a substituent as defined above and more preferably a substituent selected from alkyl and hal, and especially selected from CH_3, CH_2CH_3 and hal.

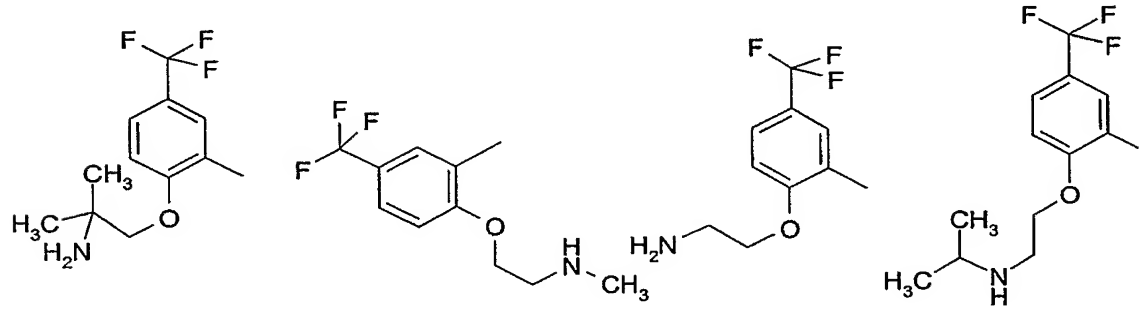
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of formulae I.1) to I.20), wherein $(R^8)_p$-Ar^1 is selected from the group consisting of 3-acetyl-phenyl, 4-acetyl-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 4-bromo-2-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-bromo-3-trifluoromethyl-phenyl, 2-chloro-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-chloro-5-trifluoromethyl-phenyl, 3-chloro-phenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-methoxy-phenyl, 3-chloro-4-methoxy-phenyl, 4-chloro-phenyl, 4-chloro-2-trifluoromethyl-phenyl, 4-chloro-3-trifluoromethyl-phenyl, 4-chloro-2-methyl-phenyl, 5-chloro-2-methyl-phenyl, 5-chloro-2-methoxy-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichloro-phenyl, 3,4-dichloro-phenyl, 3,5-dichloro-phenyl, 2,4,5-trichloro-phenyl, 4-fluoro-phenyl, 4-fluoro-3-trifluoromethyl-phenyl, 4-ethoxy-phenyl, 2-methoxy-phenyl, 2-methoxy-5-trifluoromethyl-phenyl, 4-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 3-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 4-trifluoromethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 3-methoxy-phenyl, 3-methylsulfanyl-phenyl, 4-methylsulfanyl-phenyl, o-tolyl (2-methyl-phenyl), m-tolyl (3-methyl-phenyl), p-tolyl (4-methyl-phenyl), 2,3-dimethyl-phenyl, 2,3-di-methyl-phenyl, 2,5-dimethyl-phenyl, 3,4-dimethyl-phenyl, 3,5-dimethyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 4-isopropyl-phenyl, 4-tert-butyl-phenyl and 5-tert-butyl-isoxazol-3-yl. Additionally preferred are compounds of formula I and preferably one or more of formulae I.1) to I.20),

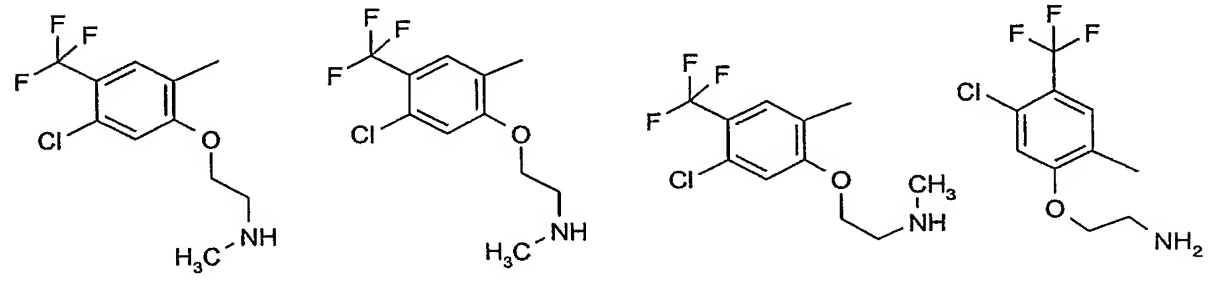
wherein $(R^8)_p$-Ar^1 is selected from the the residues given above and comprises one or two, preferably one substituent R^7 and especially one or two, preferably one substituent R^7 indicated herein as preferred, more preferred or especially preferred.

Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.20), wherein the residues $(R^8)_p$-Ar^1-$(R^7)_g$ are selected from the following formulae:

a)







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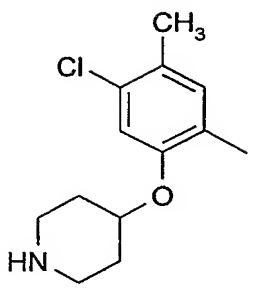
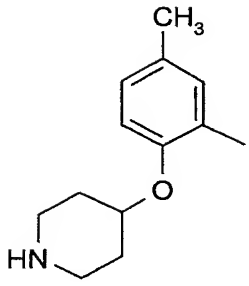
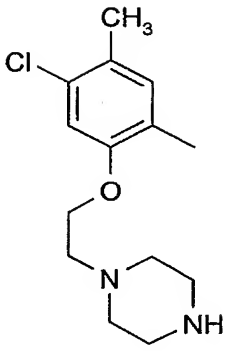
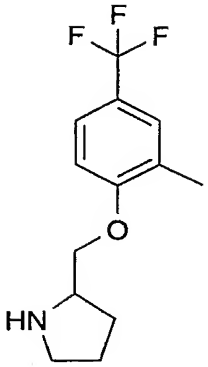
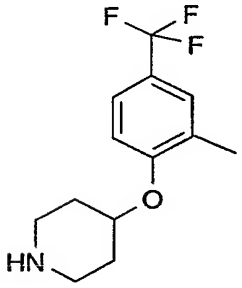
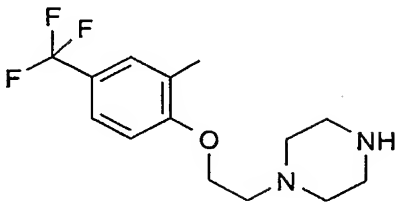


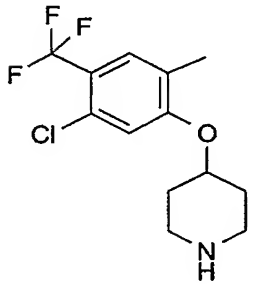


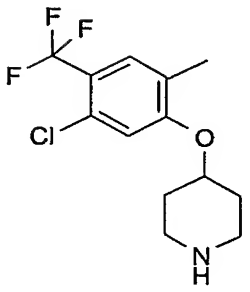


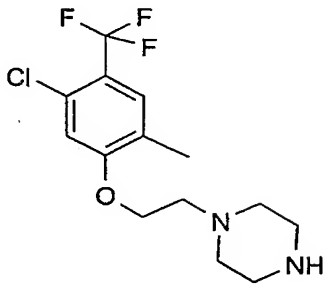




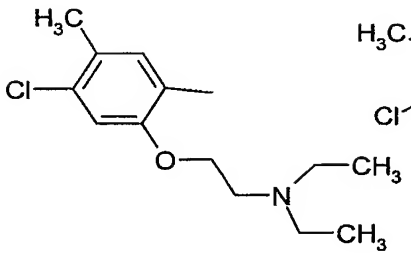


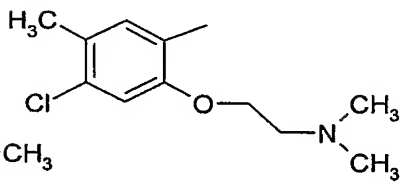


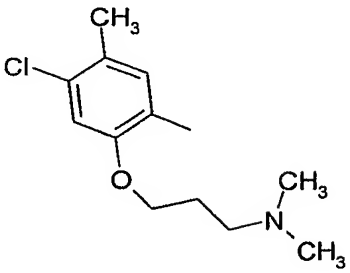


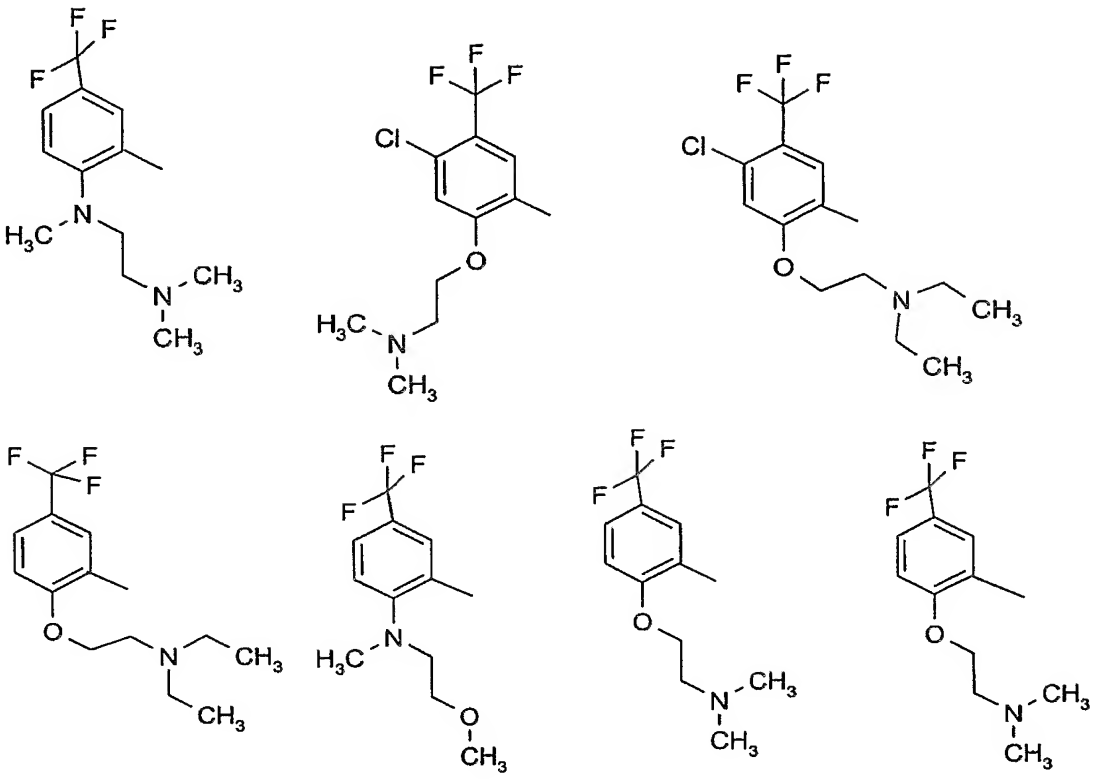


c)

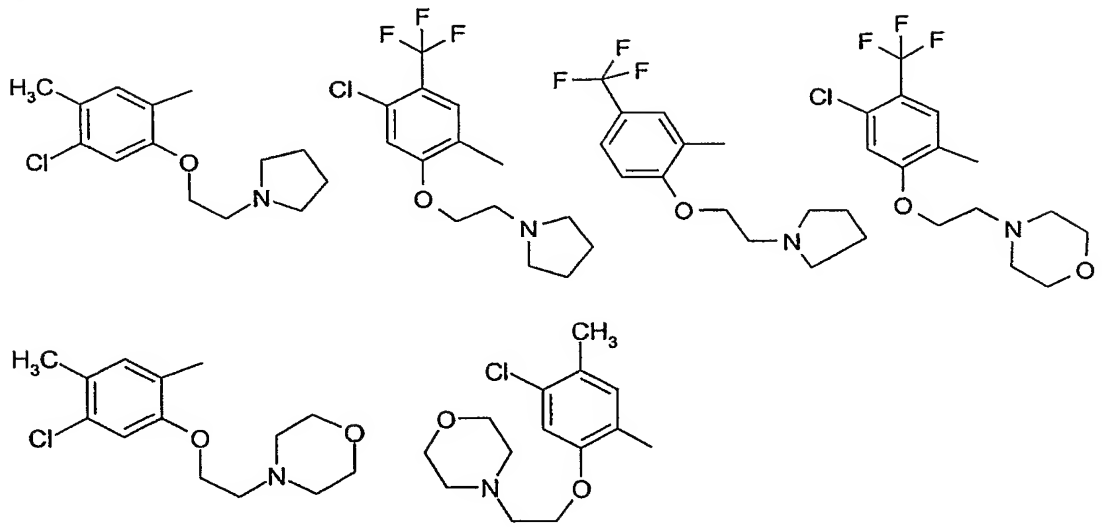




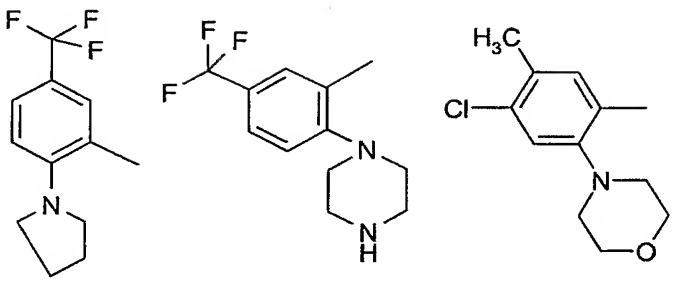




d)

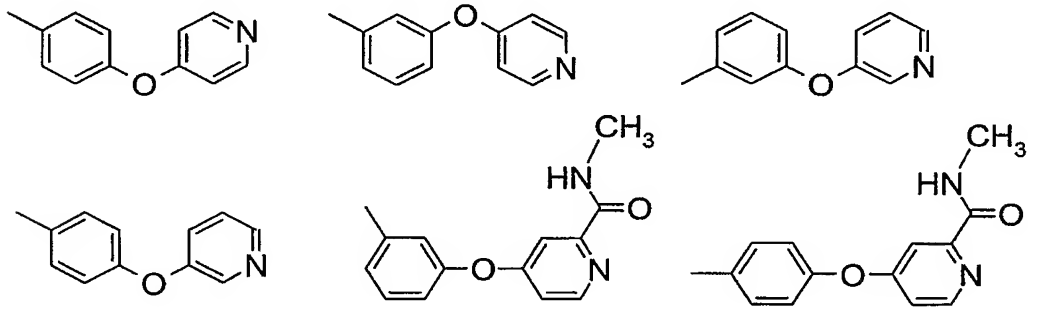


and/or e)



and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R^7 and/or R^8.

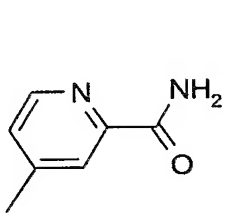
Another preferred embodiment of the instant invention relates to compounds of formula A-NH-CO-NH-B, wherein A is selected from the meanigs of $(R^8)_p$-Ar^1-$(R^7)_g$ as defined in the paragraph above, and B is selected from formulae

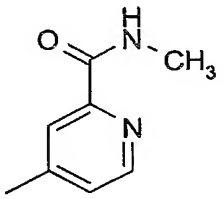


Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein $(R^8)_p$-Ar^1 is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^7 and more preferably selected from the group consisting of $O(CH_2)_kR^{13}$, $NR^{11}(CH_2)_kR^{13}$, $O(CH_2)_kOR^{13}$, $NR^{11}(CH_2)_kOR^{13}$, $O(CH_2)_kNR^{11}R^{12}$, $NR^{11}(CH_2)_kNR^{11}R^{12}$, $O(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $NR^{11}(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $O(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $NR^{11}(CH_2)_nNR^{12}(CH_2)_kNR^{11}R^{12}$, $O(CH_2)_nO(CH_2)_kOR^{11}$, $NR^{11}(CH_2)_nO(CH_2)_kOR^{12}$, $O(CH_2)_nNR^{11}(CH_2)_kOR^{12}$,

and $NR^{12}(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, and even more preferably $O(CH_2)_kR^{13}$, $NR^{11}(CH_2)_kR^{13}$, $O(CH_2)_kOR^{13}$, $NR^{11}(CH_2)_kOR^{13}$, $O(CH_2)_kNR^{11}R^{12}$, $NR^{11}(CH_2)_kNR^{11}R^{12}$. In this embodiment, n is preferably 1 or 2. In this embodiment, k is preferably 1 or 2, and especially is 2.

Another preferred embodiment of the instant invention relates to compounds of formula I and the subformulae related thereto and preferably one or more of formulae I.1) to I.20), wherein the residues Ar^2-$(R^{10})_r$ are selected from the group consisting of the following formulae:





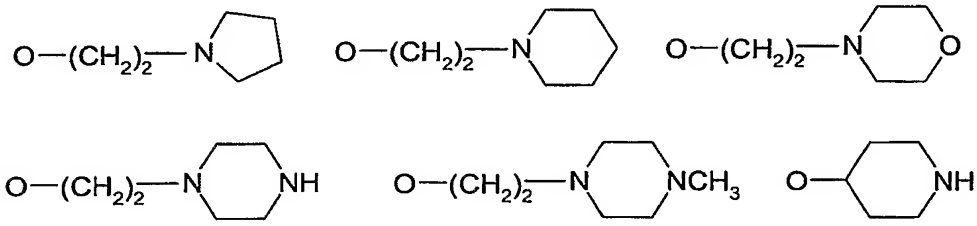
and/or residues of the structures given above that comprise one or two, preferably one additional substituent, independently selected from the meanings given for R^{10}.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein X is bonded in the para- (p-) or metha- (m-)position to the 6-membered aromatic, E, G, M, Q and U containing group that is bonded directly to the urea moiety.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^2 is a pyridinyl residue and wherein said pyridinyl residue is bonded to X in the 3- or 4-position, preferably the 4-position, relative to the nitrogen atom of the pyridinyl residue.

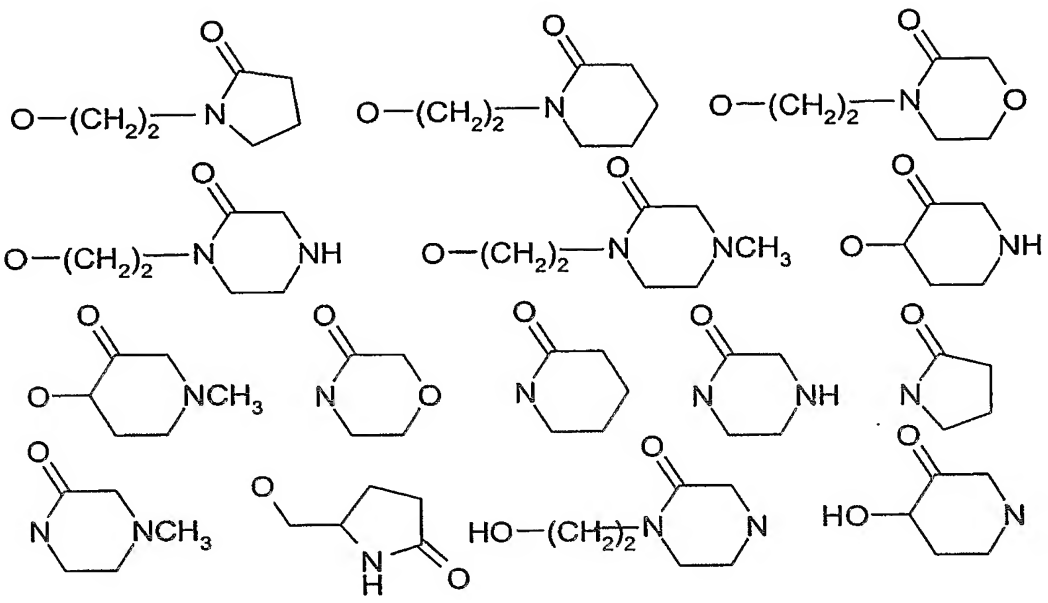
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or more substituents R^8 as defined above/below; and one or two, preferably one substituent R^7 that is selected from the group consisting of $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, $OCH_2CH_2N(CH_2CH_3)_2$, $OCH_2CH_2NHCH_3$ and/or the formulae aa):

aa)



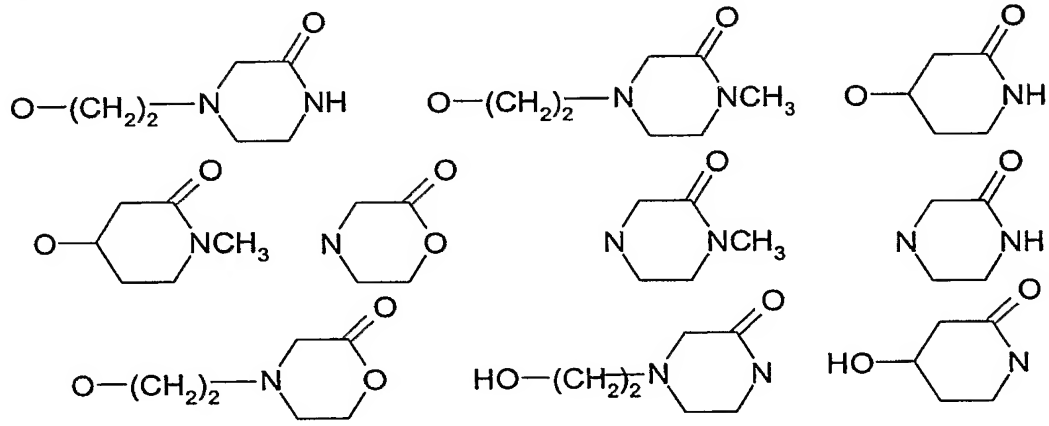
and/or bb):

bb)



and/or cc):

cc)



and/or Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is independently selected from the meanings given for R^7 in this paragraph.

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or two, preferably one substituent R^7 that is

selected from the group consisting of the formulae aa) and/or formulae bb) and/or formulae cc) as given above.

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or two, preferably one substituent R^7 that is selected from the group consisting of the formulae aa).

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or two, preferably one substituent R^7 that is selected from the group consisting of the formulae bb).

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or more substituents R^8 and one or two, preferably one substituent R^7 that is selected from the group consisting of the formulae cc).

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^1 comprises one or more substituents R^8 and wherein one or two, preferably one substituent R^8 is selected from the group consisting of SO_2CH_3, SO_2CF_3, OSO_2CH_3, OSO_2CF_3, SO_2NH_2, $SO_2NHCH(CH_3)_2$, $SO_2N(CH_3)_2$, $SO_2N(CH_2CH_3)_2$ and 4-Morpholine-4-sulfonyl.

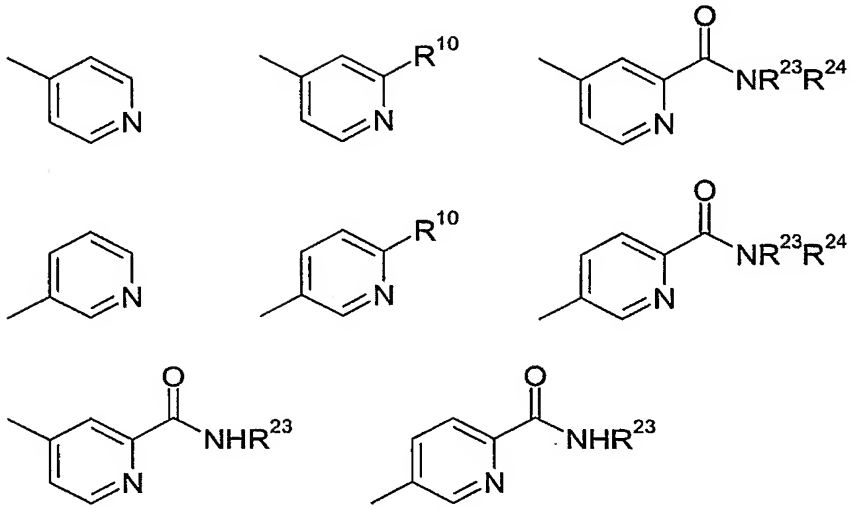
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from unsubstituted or substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are

independently selected from the definitions given for R^8, more preferably selected from alkyl, preferably methyl, ethyl, propyl and butyl, $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of methyl, ethyl, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is preferably unsubstituted C_1-C_4-alkyl and especially methyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is selected from $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20), wherein $-Ar^2-(R^{10})$ is selected from the formulae



wherein R^{10}, R^{23} and R^{24} are as defined above and below.

Another preferred embodiment of the instant invention relates to compounds of formula I and and preferably the sub formulae related thereto, wherein R^7 does not comprise OH, NH and/or NH_2 groups.

Another preferred embodiment of the instant invention relates to compounds of formula I and the sub formulae related thereto, wherein R^8 does not comprise OH, NH and/or NH_2 groups.

Another preferred embodiment of the instant invention relates to compounds of formula I and the sub formulae related thereto, wherein R^9 does not comprise OH, NH and/or NH_2 groups.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar^1 and /or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety, preferably Ar^1 and/or the phenyl group bound to the urea moiety, do not comprise a OH group in the ortho position to the urea moiety.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar^1 and /or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety, preferably Ar^1 and/or the phenyl group bound to the urea moiety, do not comprise a $-NHSO_2-$ moiety in the ortho position to the urea moiety.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar^1 and /or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety, preferably Ar^1 and/or the phenyl group bound to the urea moiety, do not comprise a $-NHSO_2-$ moiety in the ortho position to the urea moiety.

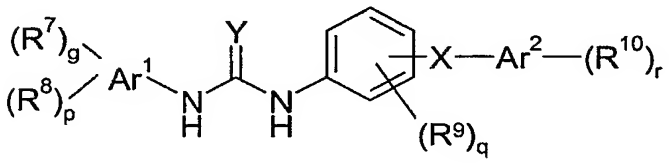
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein Ar^1 and /or the 6-membered aromatic, E, G, M, Q and U containing group bound to the urea moiety, preferably Ar^1 and/or the phenyl group bound to the urea moiety, do not comprise a moiety in the ortho position to the urea moiety having an ionizable hydrogen and a pKa of 10 or less.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably the sub formulae related thereto, wherein both the aromatic groups bound directly to the urea moiety do not comprise a substituent in the ortho position to the urea moiety, selected from OH, substituents comprising a $-NHSO_2-$ moiety, and substituents comprising moieties having an ionizable hydrogen and a pKa of 10 or less.

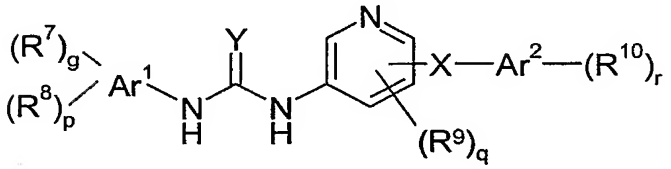
Another especially preferred embodiment of the instant invention relates to compounds of formula I, preferably the sub formulae related thereto and more preferably one or more of the sub formulae I.1) to I.20) and/or Ia to Iw,

wherein one or more features of the above and below mentioned embodiments are combined in one compound.

Subject of the present invention are therefore preferably compounds of formula I according to one or both of the formulae Ia and Ib,



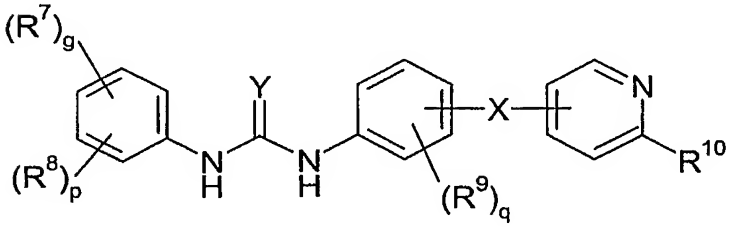
Ia



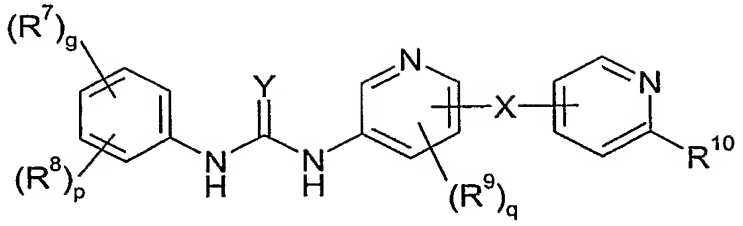
Ib

wherein Ar^1, R^7, R^8, p, g, Y, X, R^9, q, Ar^2, R^{10} and r are as defined above and below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto, and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Subject of the present invention are therefore especially preferred compounds of formula I according to one or both of the formulae Ic and Id,



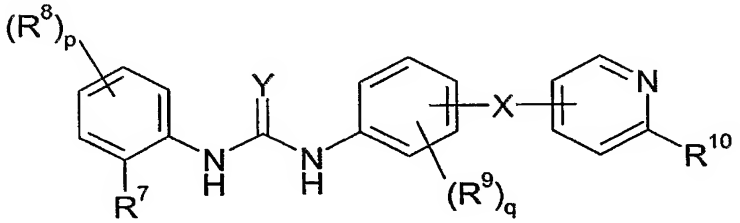
Ic



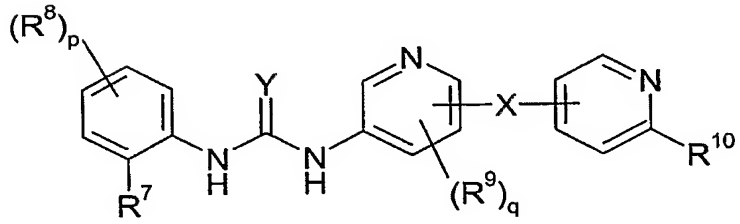
Id

wherein R^7, g, R^8, p, Y, X, R^9 and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto;

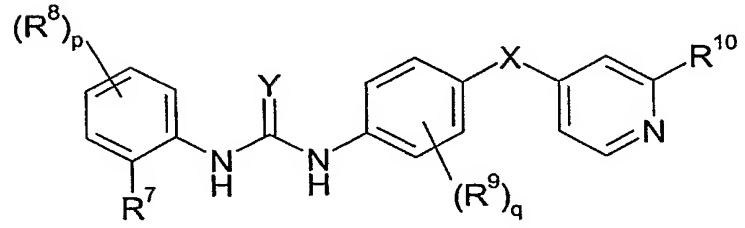
and/or compounds of formula I according to one or more of the formulae Ie to Iw,



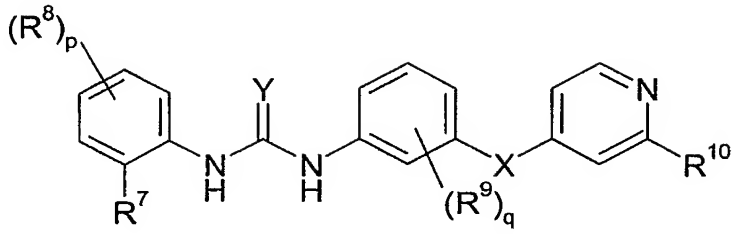
Ie



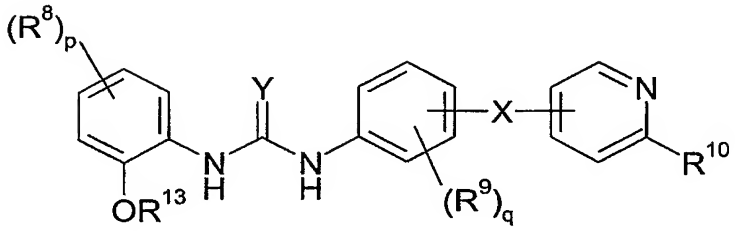
If



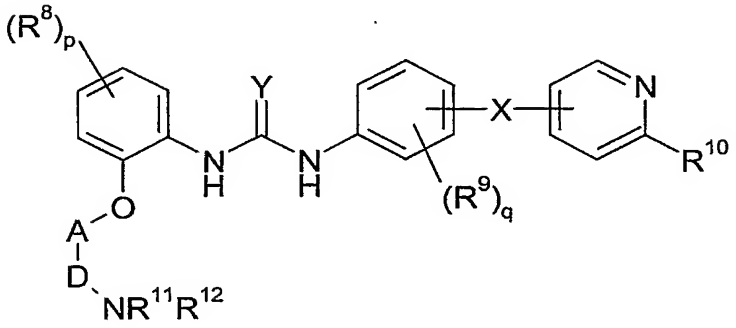
Ig



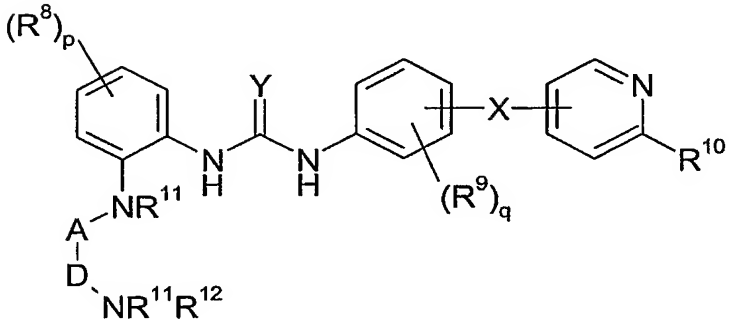
Ih



Ii



Ij



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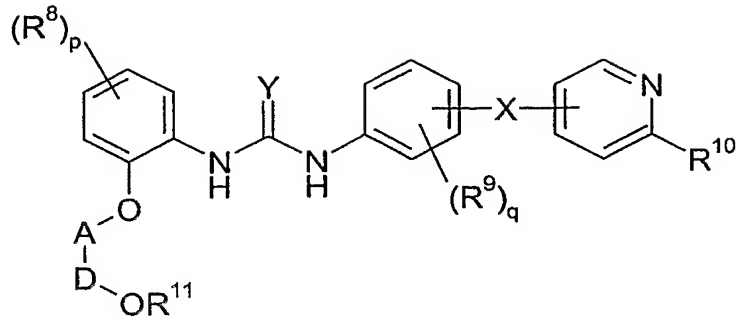

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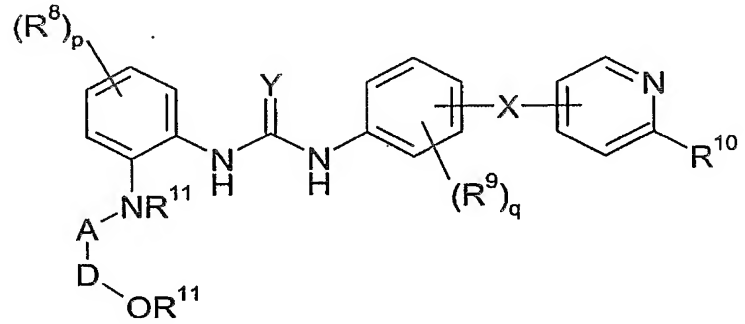
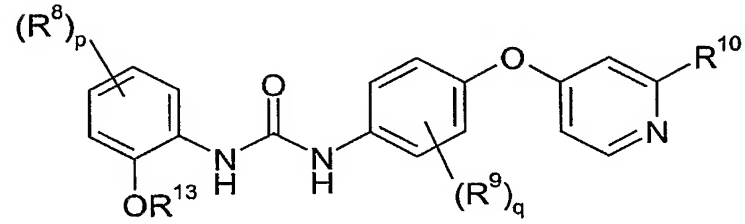
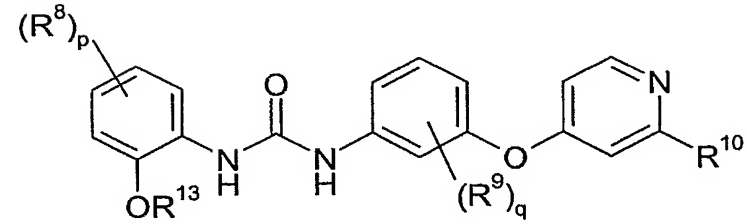


Im



In



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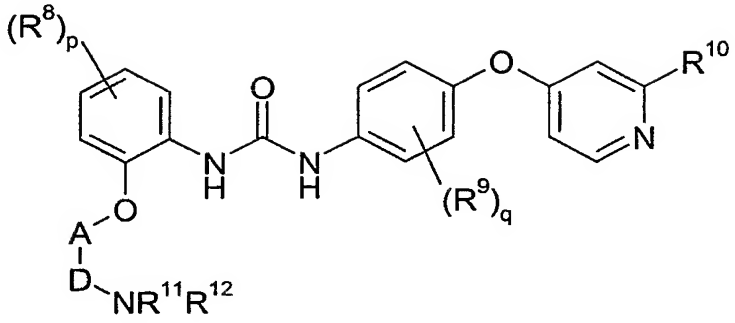
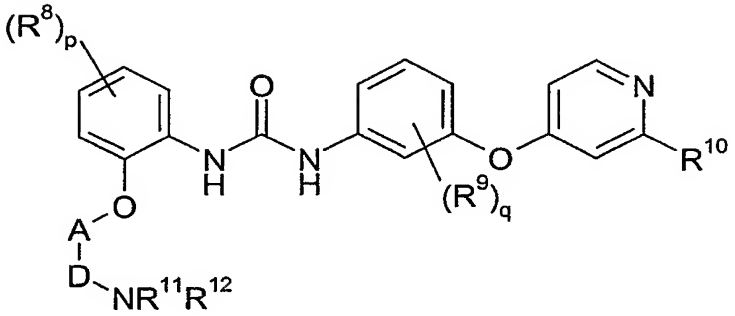
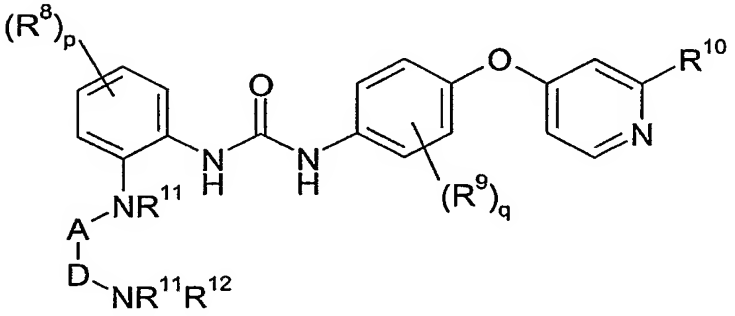


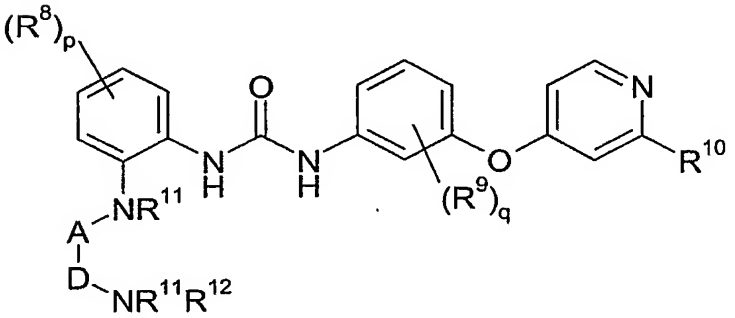
Ip



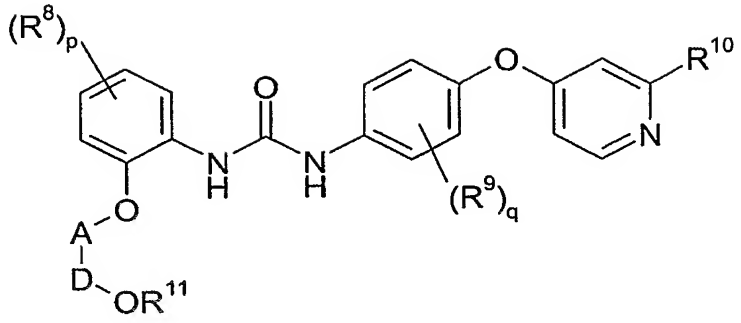
Iq



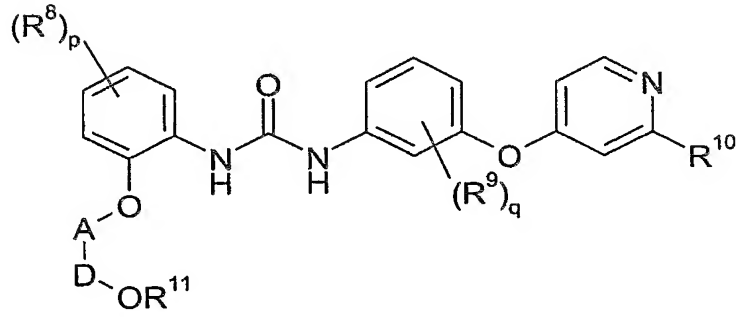
Ir



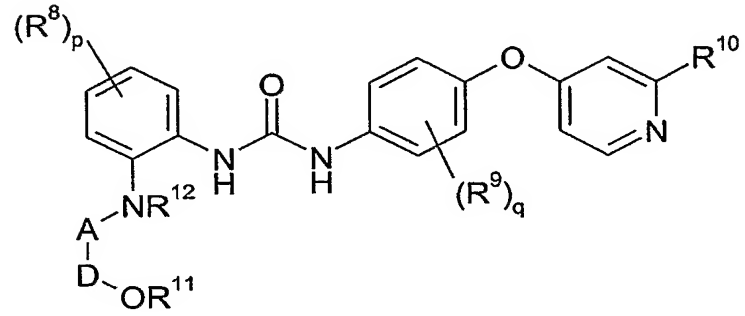
Is



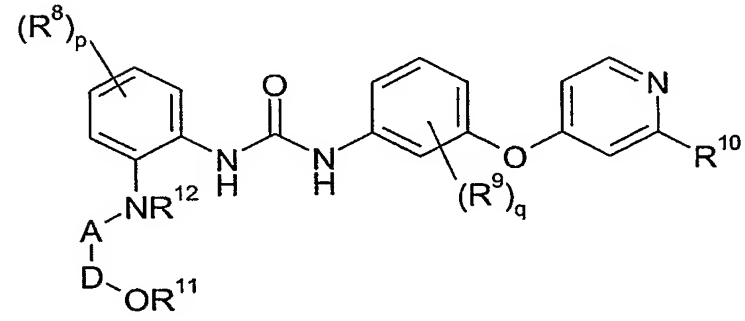
It



Iu



Iv



Iw

wherein R^7, R^8, R^{11}, R^{12}, R^{13}, Y, X, R^9, p and q are as defined above and below, R^{10} is H or as defined above/below, and preferably as defined in sub formulae I.1) to I.20) and/or the embodiments related thereto, and A and D are CR^5R^6, and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20) and Ia to Ih, wherein R^{10} is a substituted carbamoyl moiety $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are independently selected from the definitions given for R^8, more preferably selected from CH_3 and $(CH_2)_nNR^{11}R^{12}$, wherein R^{11}, R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of CH_3, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH, $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.20) and Ii and In, wherein R^{13} is $(CH_2)_mHet$, wherein Het is preferably saturated heterocyclyl and wherein m is preferably 0, 1or 2.

Another preferred embodiment of the instant invention relates to compounds of sub formulae Ij to Im and Ip to Iw, wherein A and D are independently selected from CH_2 and $C(CH_3)_2$.

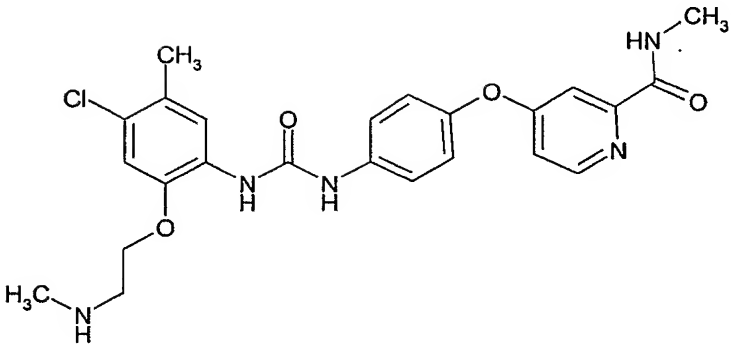
It is understood that when a residue, for example R^8, R^9, R^{10} or R^{14} or R^{23}, is comprised twice or more times in one or more of the formulae I and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For

example, R^{11} and R^{12} are defined to be independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$. Then $(CH_2)_nNR^{11}(CH_2)_mNR^{12}R^{12}$ can be $(CH_2)_nNA(CH_2)_mNA_2$ (if R^{11} = A, R^{12} = A and R^{12} = H) as well as $(CH_2)_nNA(CH_2)_mNHA$ (if R^{11} = A, R^{12} = H and R^{12} = A or $(CH_2)_nNA(CH_2)_mNH(CH_{2m}Het$ (if R^{11} = A, R^{12} = H and R^{12} = $(CH_2)_mHet$). Accordingly, if a compound of formula I comprises one residue R^8, R^9 and R^{10}, then for example R^8, R^9 and R^{10} can all be $(CH_2)_nCOOR^{13}$, wherein all residues R^{13} are the same (for example CH_2Hal, wherein Hal is Cl; then all residues R^8, R^9 and R^{10} are the same) or different (for example CH_2Hal, wherein in R^8 Hal is Cl; in R^9 Hal is F; and in R^{10} Hal is Br; then all residues R^8, R^9 and R^{10} are different); or for example R^8 is $(CH_2)_nCOOR^{13}$, R^9 is NO_2 and R^{10} is $(CH_2)_nSR^{11}$, wherein R^{11} and R^{13} can be the same (for example both can be H or both can be A which is methyl) of different (for example R^{11} can be H and R^{13} can be A which is methyl).

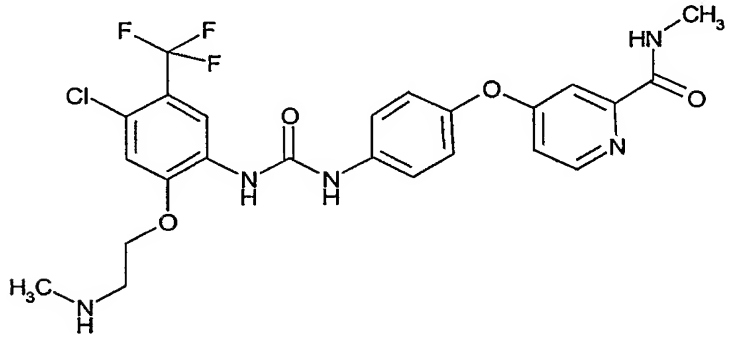
If not stated otherwise, reference to compounds of formula I and formula I also includes the sub formulae related thereto, especially sub formulae I.1) to I.20) and Ia to Iw.

Subject of the instant invention are especially those compounds of formula I and/or formula I, in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

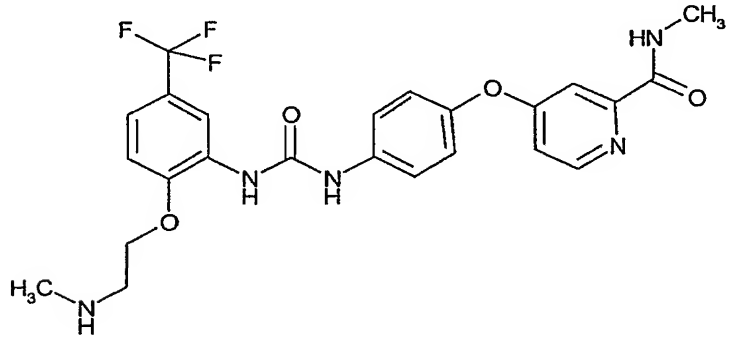
Especially preferred as compounds according to the invention are the compounds given below:



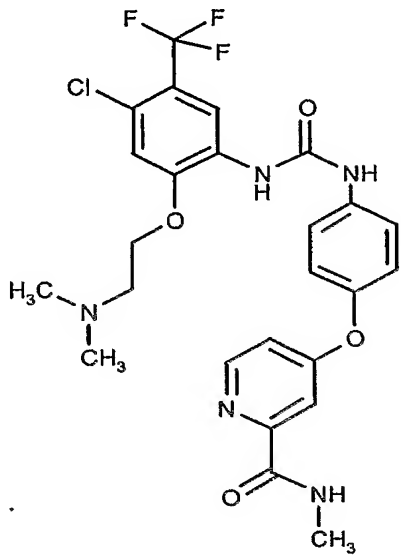
4-(4-{3-[4-Chloro-5-methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 483.95; Rt = 2.08)



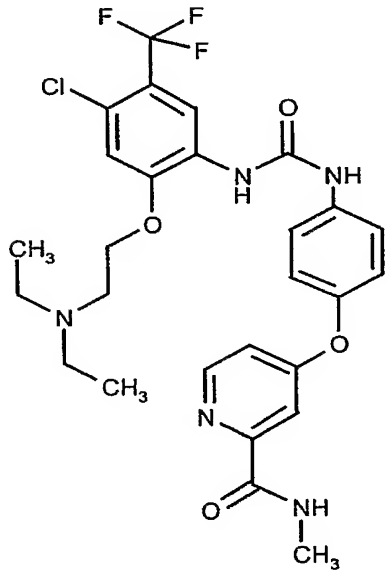
4-(4-{3-[Chloro-(2-methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 537.92; Rt = 2.21)



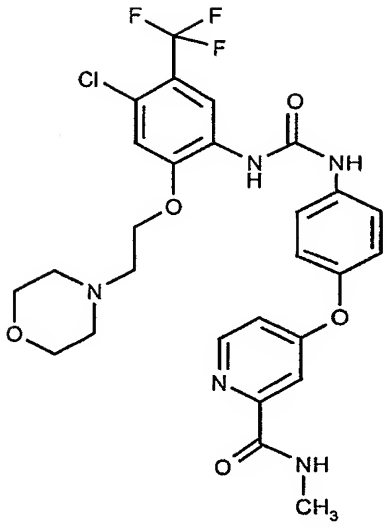
4-(4-{3-[(2-Methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 503.48; Rt = 2.09)



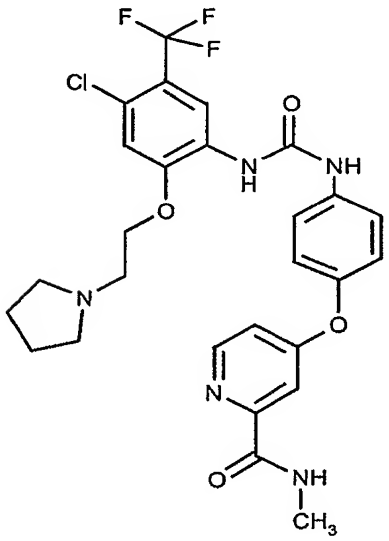
4-(4-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 551.95; Rt = 2.25)



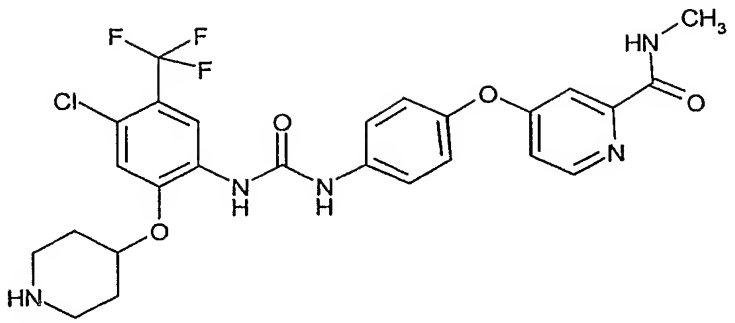
4-(4-{3-[Chloro-(2-diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 580.00; Rt = 2.29)



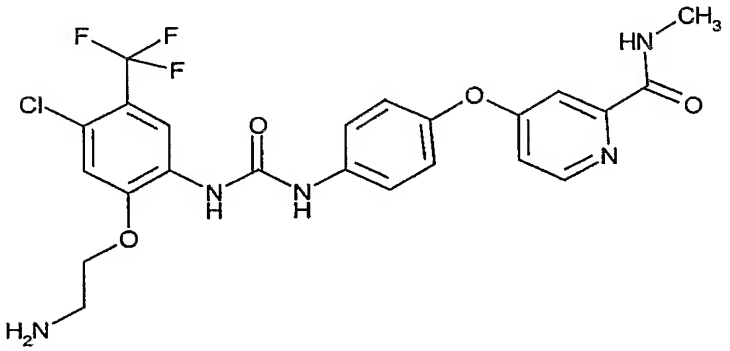
4-(4-{3-[Chloro-(2-morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 593,99. Rt = 2.26)



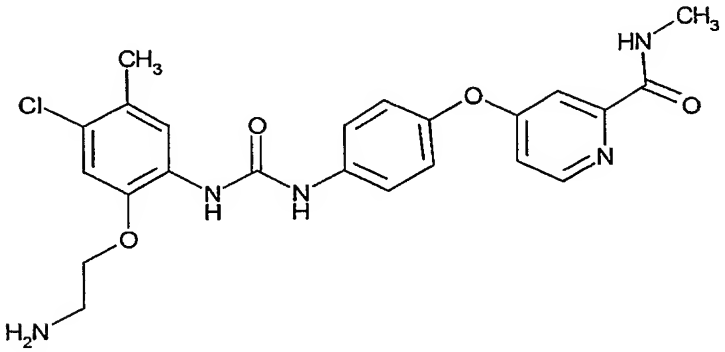
4-(4-{3-[Chloro-(2-pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 577.99; Rt = 2.27)



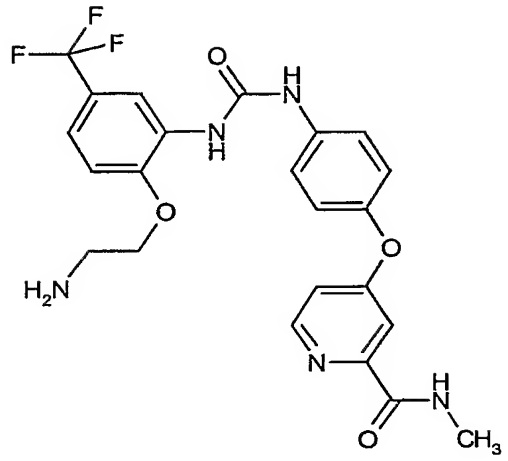
4-(4-{3-[Chloro-(piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 563.96; Rt = 2.29)



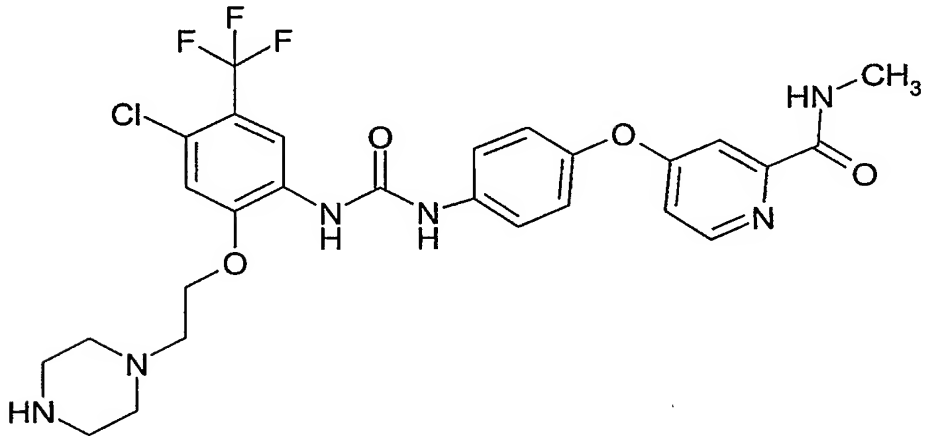
4-(4-{3-[(2-Amino-ethoxy)-chloro-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 523.90; Rt = 2.21)



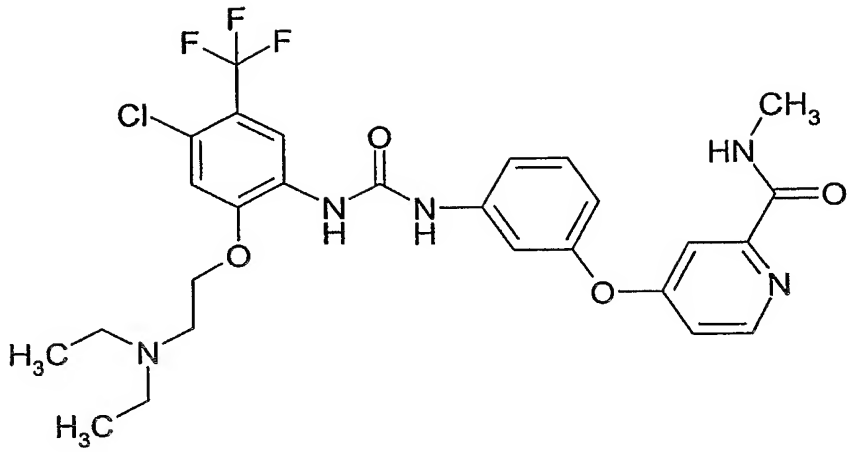
4-(4-{3-[2-(2-Amino-ethoxy)-4-chloro-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 469.93; Rt = 2.03)



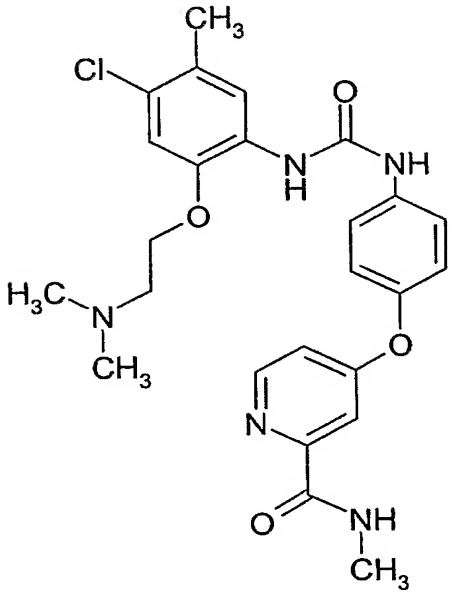
4-(4-{3-[(2-Amino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 489.45; Rt = 2.11);



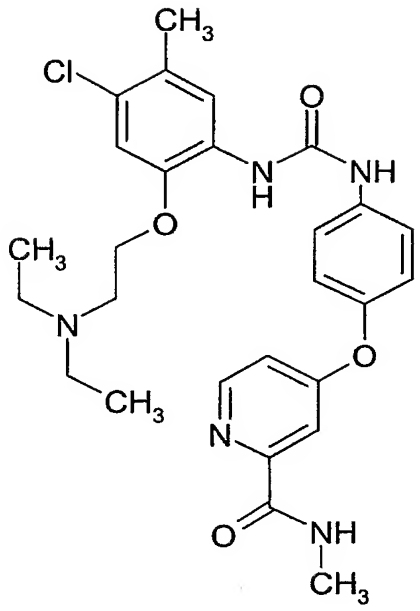
4-(4-{3-[Chloro-(2-piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 593.00; Rt = 2.24);



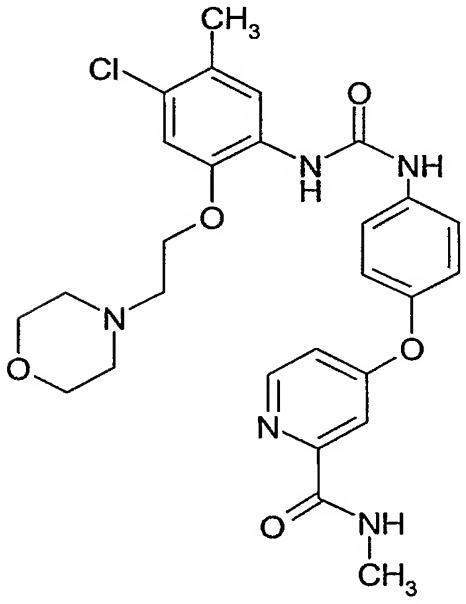
4-(3-{3-[Chloro-(2-diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 580.00; Rt = 2.29);



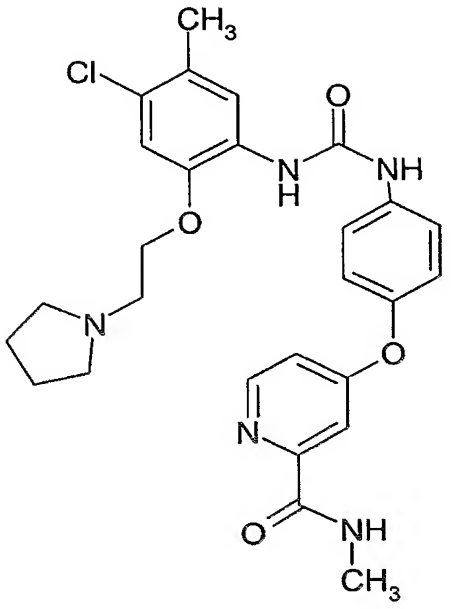
4-(4-{3-[4-Chloro-2-(2-dimethylamino-ethoxy)-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylicacid methylamide (MW = 497.98; Rt = 2.93[a]);



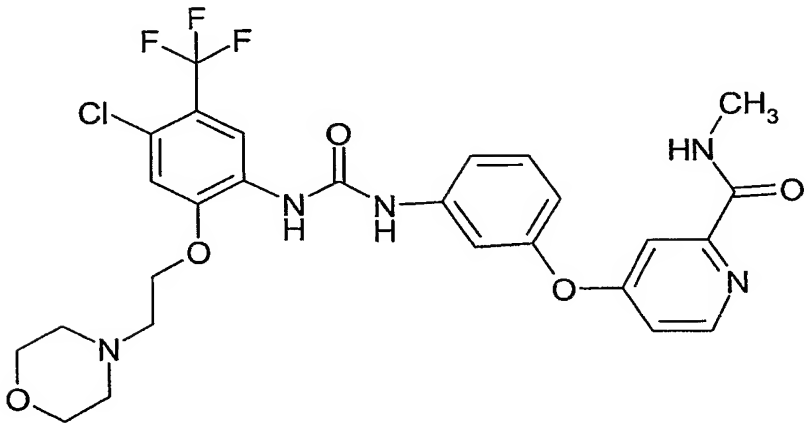
4-(4-{3-[4-Chloro-2-(2-diethylamino-ethoxy)-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylicacid methylamide (MW = 526.03; Rt = 2.97[a]);



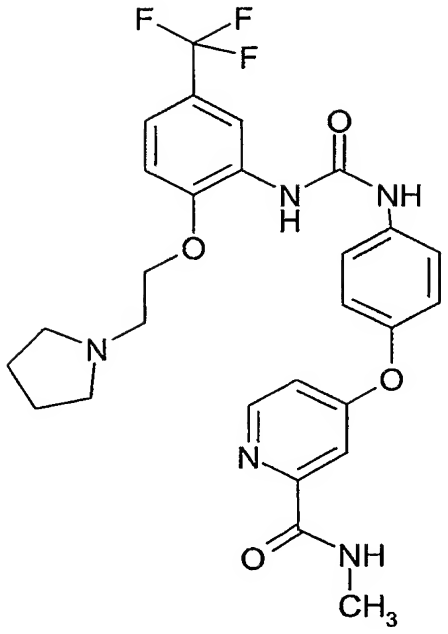
4-(4-{3-[4-Chloro-5-methyl-2-(2-morpholin-4-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 540.02; Rt = 2.93[a]);



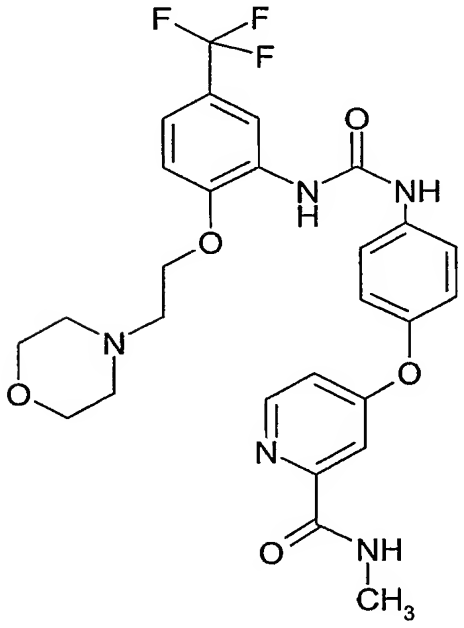
4-(4-{3-[4-Chloro-5-methyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 524.02; Rt = 2.99[a]);



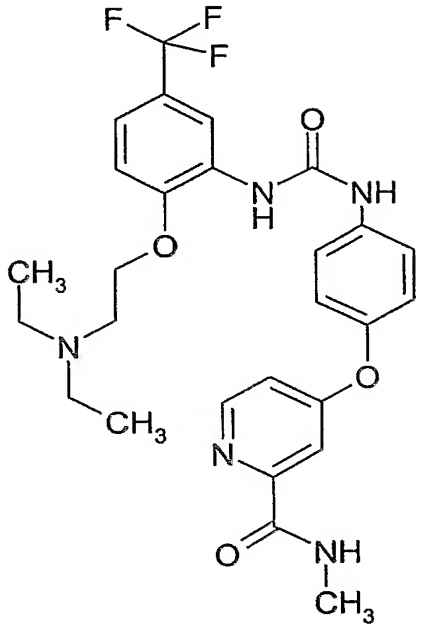
4-(3-{3-[Chloro-(2-morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 593.99; Rt = 2.27);



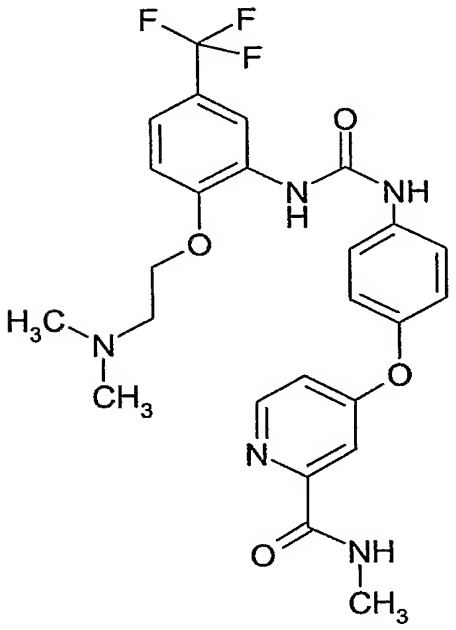
4-(4-{3-[(2-Pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 543.54; Rt = 3.01[a]);



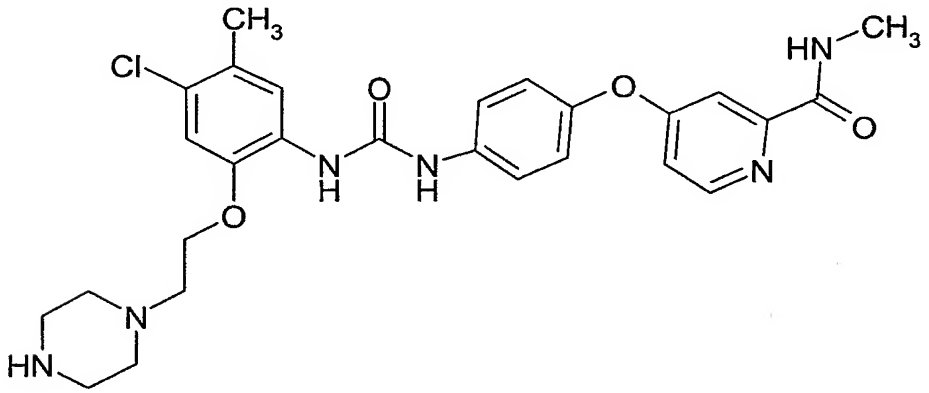
4-(4-{3-[(2-Morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 559.54; Rt = 2.98[a]);



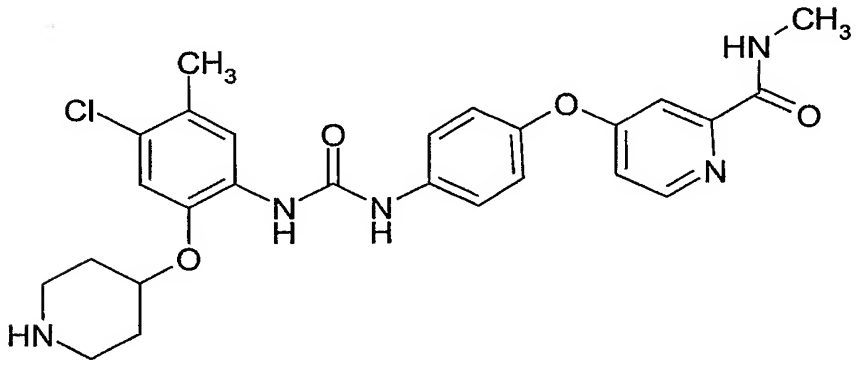
4-(4-{3-[(2-Diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 545.56; Rt = 2.99[a]);



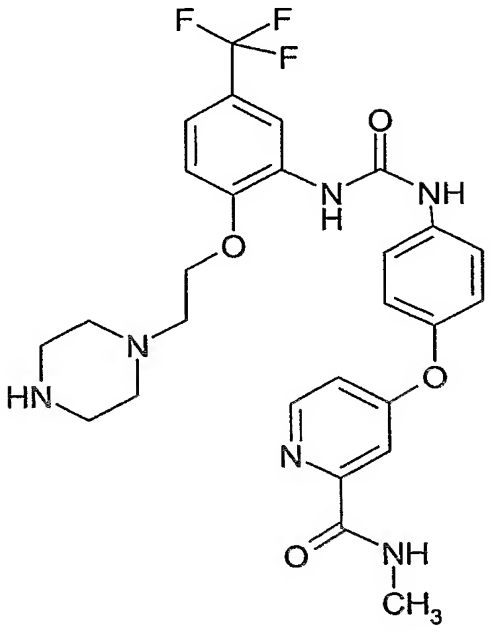
4-(4-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 517.51; Rt = 2.12);



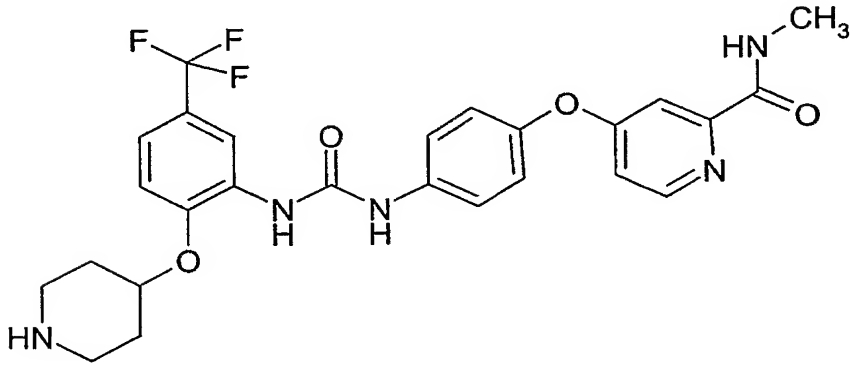
4-(4-{3-[4-Chloro-5-methyl-2-(2-piperazin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 539.03; Rt = 2.04);



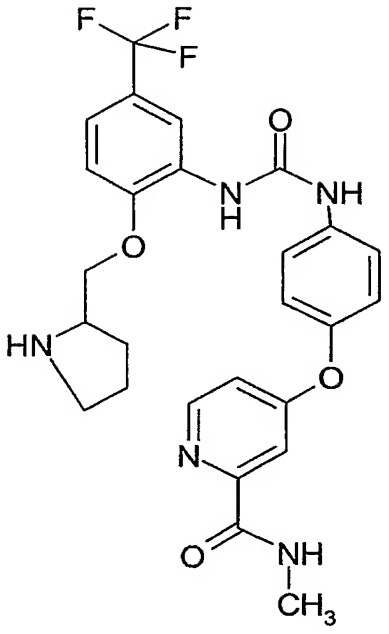
4-(4-{3-[4-Chloro-5-methyl-2-(piperidin-4-yloxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 509.99; Rt = 2.14);



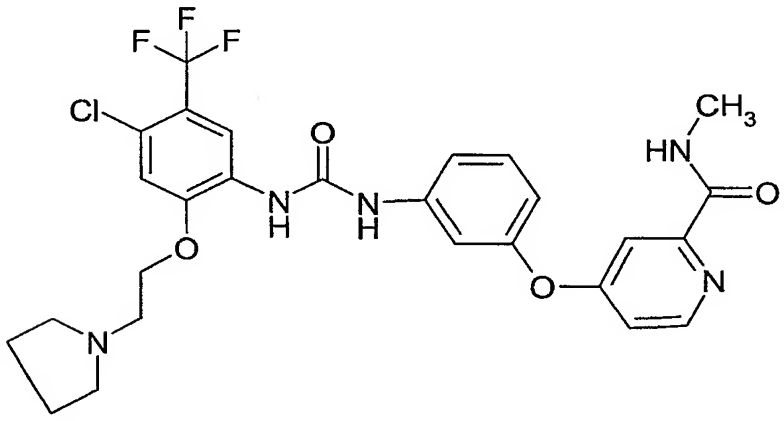
4-(4-{3-[(2-Piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 558.56; Rt = 2.11);



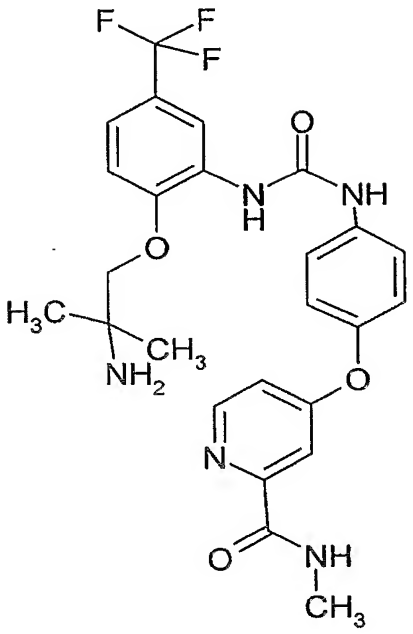
4-(4-{3-[(Piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 529.52; Rt = 2.17);



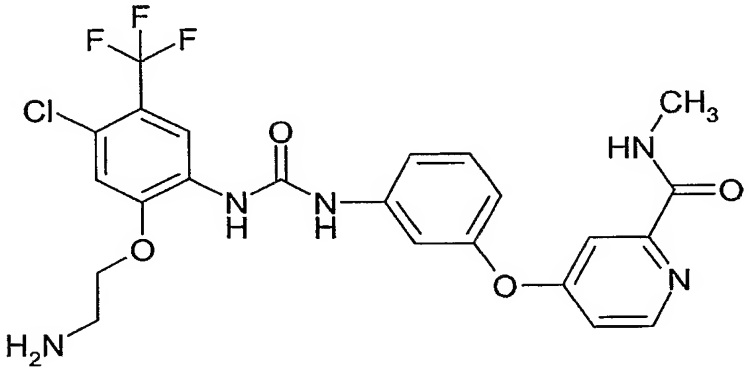
4-(4-{3-[(Pyrrolidin-2-ylmethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 529.52; Rt = 2.14);



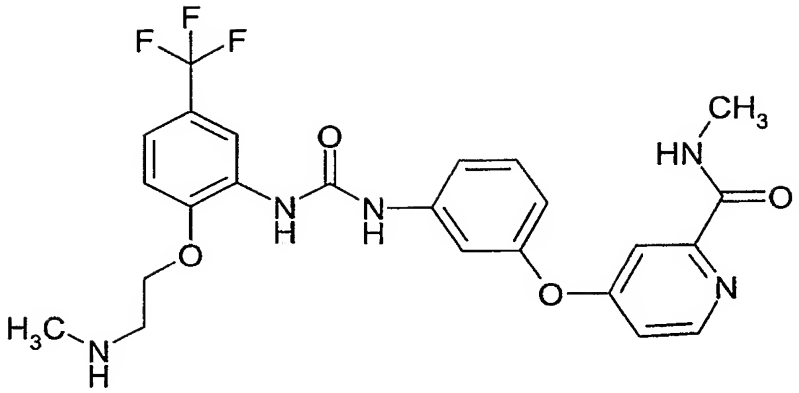
4-(3-{3-[Chloro-(2-pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 529.52; Rt = 2.27);



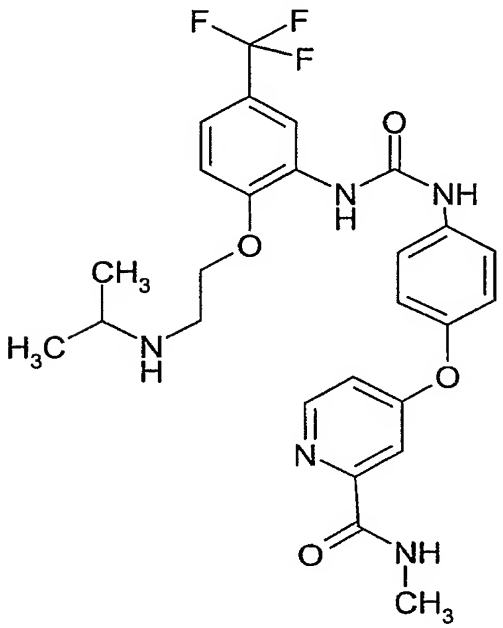
4-(4-{3-[(2-Amino-2-methyl-propoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 517.51; Rt = 2.13);



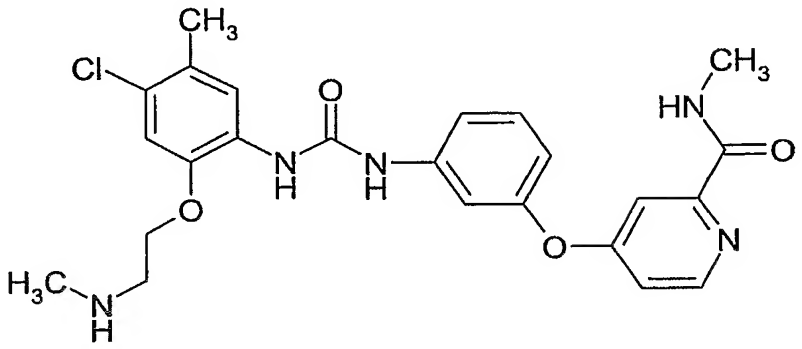
4-(3-{3-[(2-Amino-ethoxy)-chloro-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 523.90; Rt = 2.23);



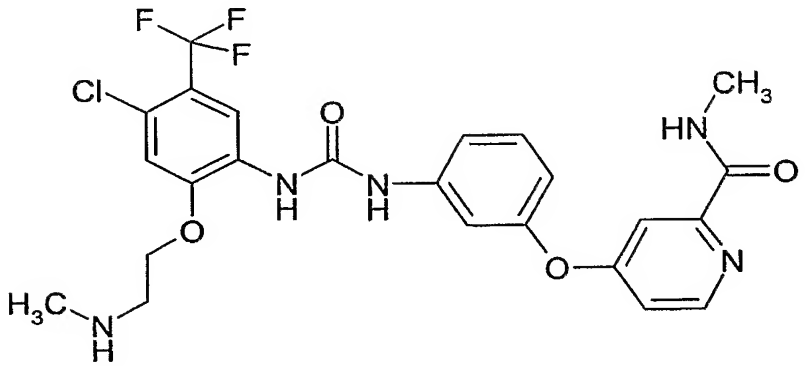
4-(3-{3-[(2-Methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 503.48; Rt = 2.14);



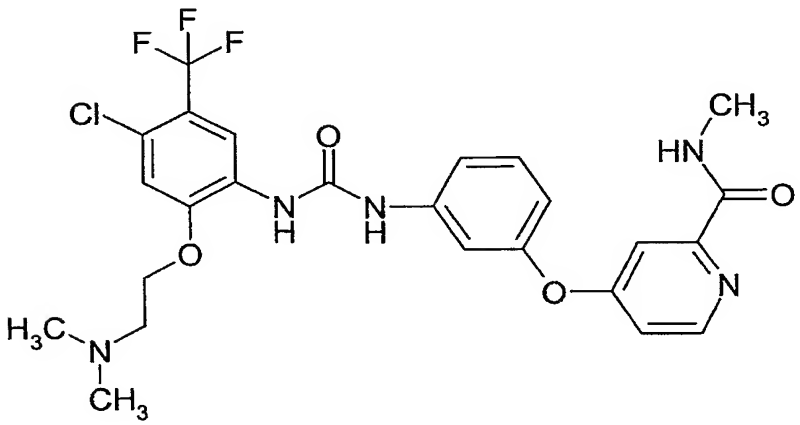
4-(4-{3-[(2-Isopropylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 531.48; Rt = 2.14);



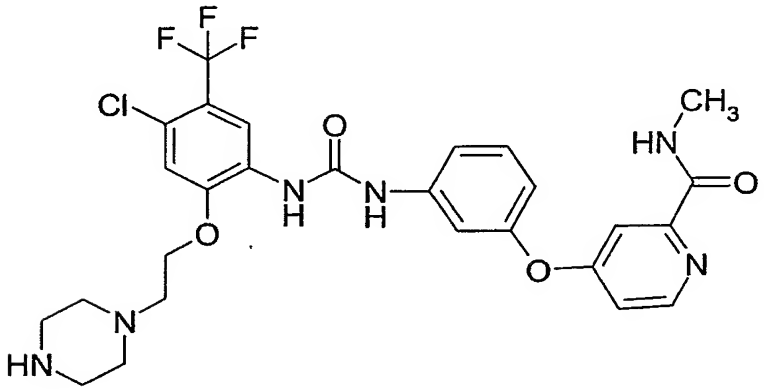
4-(3-{3-[4-Chloro-5-methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 483.95; Rt = 2.11);



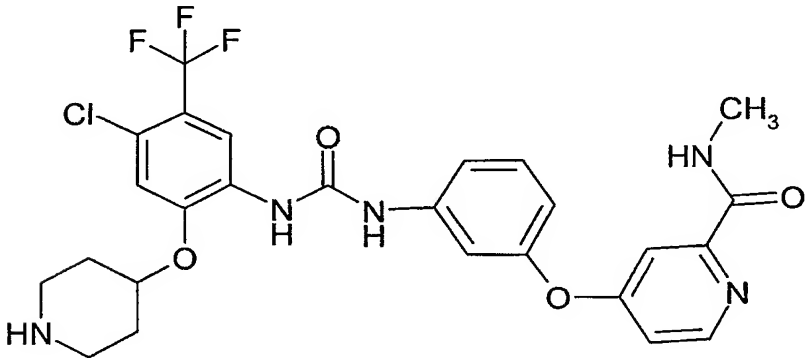
4-(3-{3-[Chloro-(2-methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 531.53; Rt = 2.26);



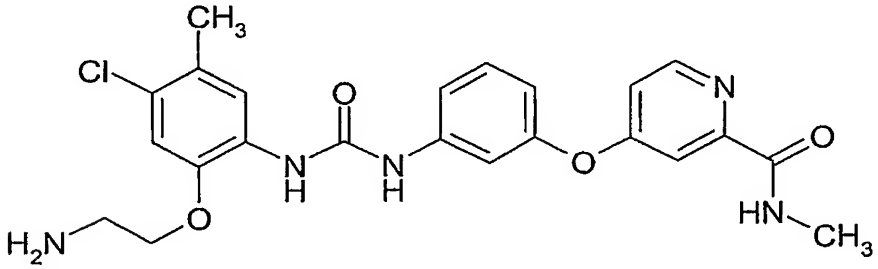
4-(3-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 551.95; Rt = 2.25);



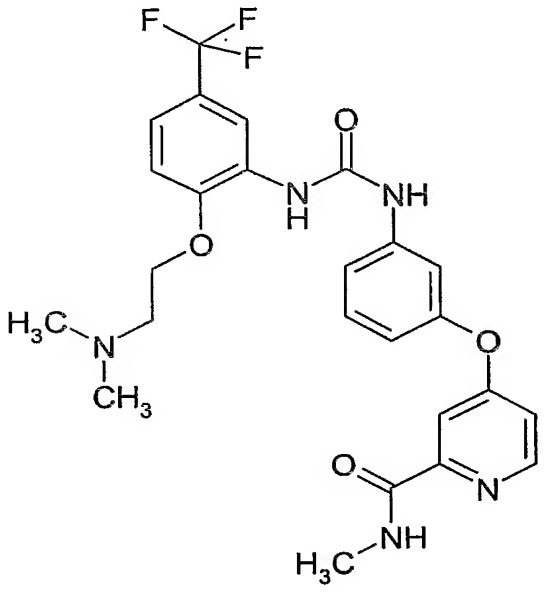
4-(3-{3-[Chloro-(2-piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 593.00; Rt = 2.2);



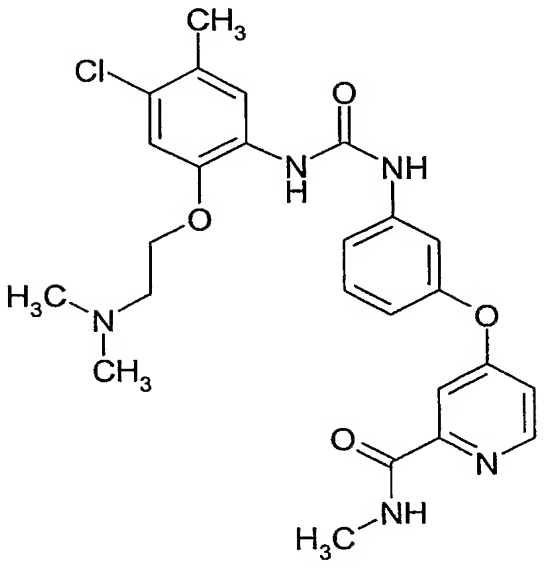
4-(3-{3-[Chloro-(piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 563.96; Rt = 2.31);



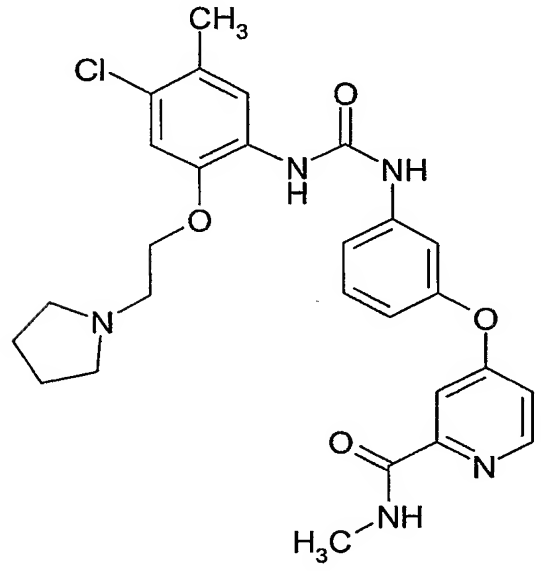
4-(3-{3-[2-(2-Amino-ethoxy)-4-chloro-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 469.93; Rt = 2.07);



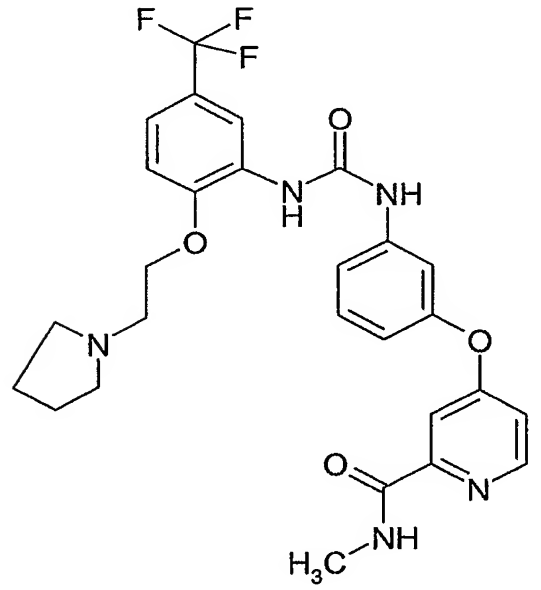
4-(3-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 517.51; Rt = 2.15);



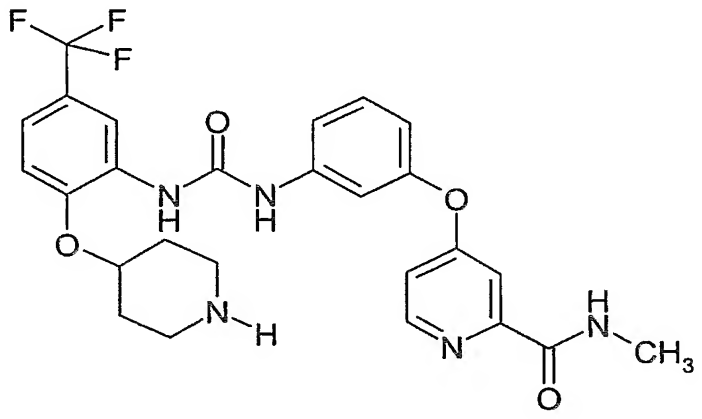
4-(3-{3-[4-Chloro-2-(2-dimethylamino-ethoxy)-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylicacid methylamide (MW = 497.98; Rt = 2.11);



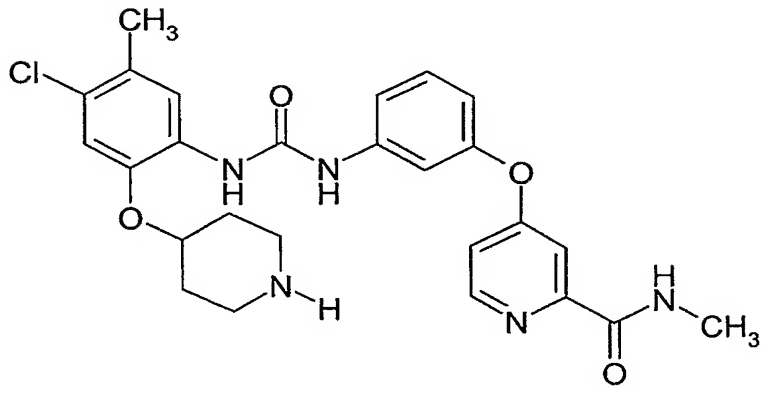
4-(3-{3-[4-Chloro-5-methyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 524.02; Rt = 2.21);



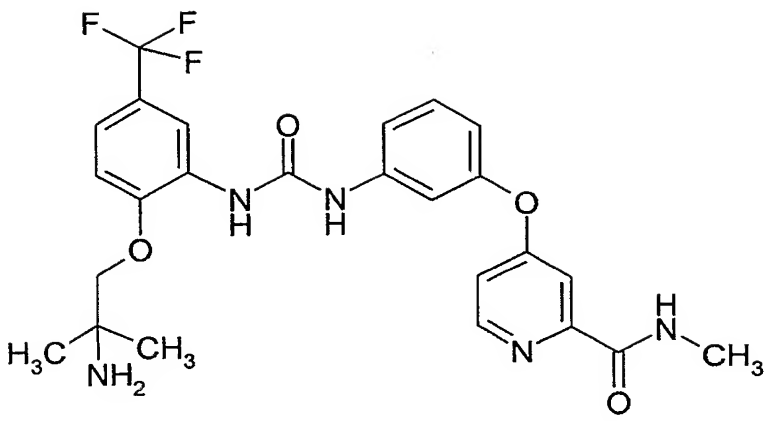
4-(3-{3-[(2-Pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 543.54; Rt = 2.2);



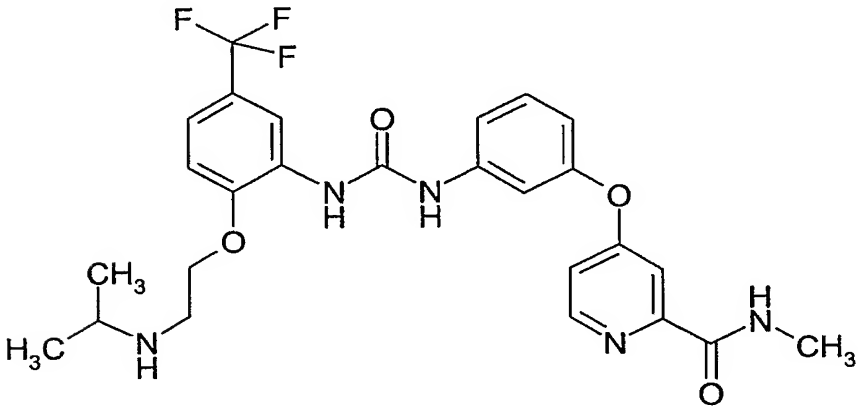
4-(3-{3-[(Piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 529.52; Rt = 2.2);



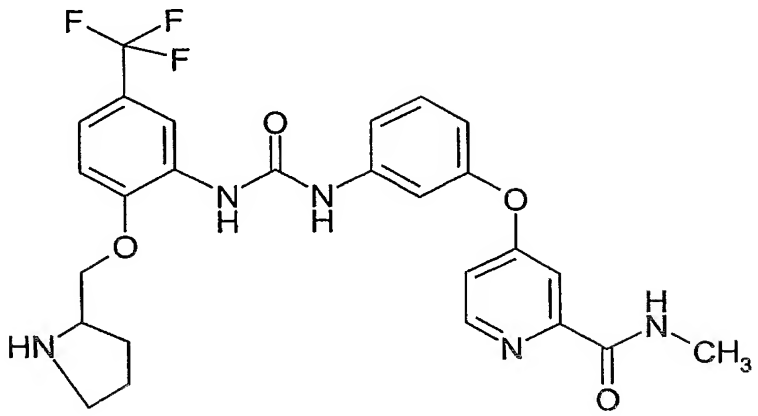
4-(3-{3-[4-Chloro-5-methyl-2-(piperidin-4-yloxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide (MW = 509.99; Rt = 2.17);



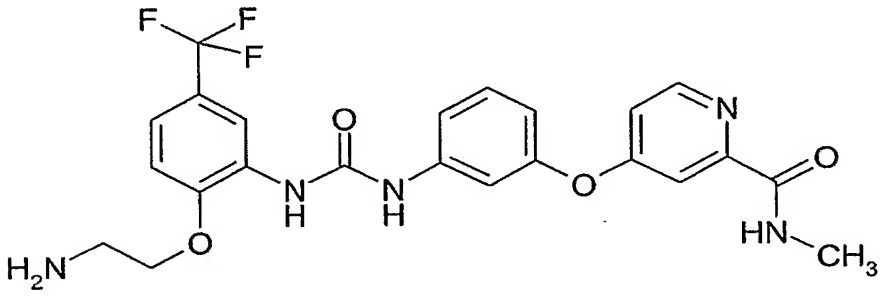
4-(3-{3-[(2-Amino-2-methyl-propoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 517.51; Rt = 2.17);



4-(3-{3-[(2-Isopropylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 531.53; Rt = 2.21);



4-(3-{3-[(Pyrrolidin-2-ylmethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 529.52; Rt = 2.22);



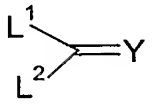
4-(3-{3-[(2-Amino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide (MW = 489.45; Rt = 2.15);

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and more preferred the salts and/or solvates thereof, and especially preferred the physiologically acceptable salts and/or solvates thereof.

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

a) a compound of formula II,

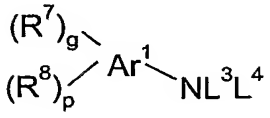


wherein

L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

is reacted with

b) a compound of formula III



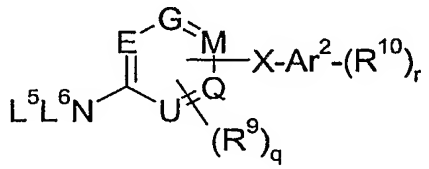
III

wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^7, R^8, g, p and Ar^1 are as defined above and below,

and

c) a compound of formula IV,



IV

wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, G, M, Q, U, R^9, q, X, Ar^2, R^{10} and r are as defined above and below,

and optionally

d) isolating and/or treating the compound of formula I obtained by said reaction withan acid, to obtain the salt thereof.

The compounds of the formula I and also the starting materials for their preparation can be prepared by methods known per se, i. e. as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

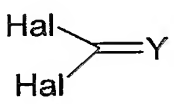
The compounds according to the invention can be manufactured or produced in an advantageous manner according to the methods of manufacture as described herein.

The reaction for the manufacture of compounds of formula I as described herein can be characterised as a carbonylation reaction of amines or the reaction of amines with carbon dioxide, carbon disulphide or derivatives or analogues thereof.

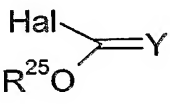
According to one aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 are preferably selected independently from one another from suitable leaving groups. Suitable leaving groups L^1 and L^2 for this type of reaction are known in the art, for example from the literature cited above. More preferably, L^1 and L^2 are independently selected from halogen, OR^{25} and $O\text{-}SO_2\text{-}R^{25}$. The residue R^{25} is preferably selected from substituted or unsubstituted alkyl groups and substituted or unsubstituted aryl groups, preferably substituted alkyl groups and substituted aryl groups. Preferred as alkyl groups in this respect are C1-C4- alkyl groups. Preferred as aryl group in this respect is phenyl. Suitable substituents for substituted alkyl groups are preferably selected from electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted alkyl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. Suitable substituents for substituted aryl groups are preferably selected from alkyl groups, preferably C_1 –C_4 alkyl groups, and electronegative and/or electron withdrawing groups. Examples of electronegative and/or electron withdrawing groups for substituted aryl groups include, but are not limited to halogen, especially Cl and/or F, cyano groups and nitro groups. If R^{25} is an unsubstituted alkyl group, it is preferably methyl. If R^{25} his a substituted alkyl group, it is preferably CF_3 or CCl_3. If R^{25} is an unsubstituted aryl group, it is preferably phenyl. If R^{25} is a substituted aryl group, it is preferably selected from para- tolyl- (i. e. p-Me-C_6H_4) and para-Nitro-phenyl (i.e the p-O_2N-C_6H_4).

Even more preferably, the leaving groups OR^{25} are selected from the para-Tosyl- (i. e. p-Me-C_6H_4-SO_3-) group, the para-Nitro-phenolate- (i.e the p-O_2N-C_6H_4-O-) group and the triflate- (i. e. the F_3C-SO_3-) group.

Preferably, compounds of formula II, wherein L^1 and L^2 are selected independently from one another from suitable leaving groups, are selected from compounds IIa, IIb and IIc,

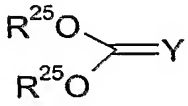


IIa



IIb

and

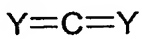


IIc

wherein Y, Hal and OR^{25} are as described above/below.

According to another aspect of the method according to the invention, in the compounds of formula II, L^1 and L^2 together represent a leaving group. In this aspect, L^1 and L^2 together preferably represent Y as the leaving group, wherein the leaving group Y is as defined above/below and more preferably is O or S.

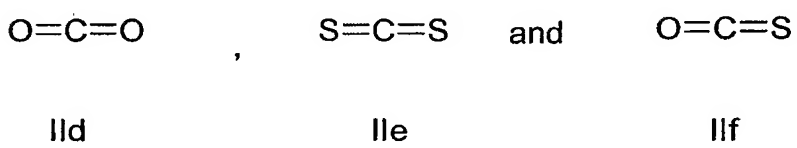
According to this aspect of the method according to the invention, the compound of formula II is a compound of formula II',



II'

wherein each Y is independently selected from the meaning given above/below, and especially is independently selected from O and S.

According to this aspect of the method according to the invention, the compound of formula II is preferably selected from compounds of formula IId, formula IIe and formula IIf,



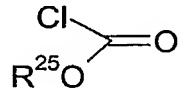
IId IIe IIf

more preferably of compounds of formula IId and formula IIe. In this aspect, compounds of formula IIa are especially preferred.

In compounds of formula II, Y is preferably selected from O and S, and more preferably is O.

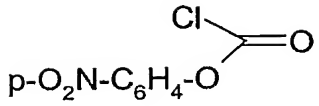
If compounds of formula II are desired wherein Y is other than O, it can be advantageous however to carry out the reaction according to the invention selecting a compound of formula II wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a $C=NR^{21}$, $C=C(R^{22})-NO_2$, $C=C(R^{22})-CN$ or $C=C(CN)_2$ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

In the method of manufacture according to the invention, the compound of formula II is even more preferably a compound of formula IIg,



IIg

wherein R^{25} is as defined above/below, and especially a compound of formula IIh,



IIh.

In the compounds of formula IV, L^1, L^2 and/or L^3 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na K are especially preferred. In case of multi-valent metal ions, the metal ions and the compounds of formula IV form a complex containing one or more compounds of formula IV and one or more metal ions wherein the ratio between compounds of formula IV and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality. Preferably, at least one of L^1, L^2 and L^3, more preferred at least two of L^1, L^2 and L^3 and even more preferred L^1, L^2 and L^3 are hydrogen.

In detail, the reaction of the compounds of formula II, formula III and formula IV is carried out in the presence or absence of a preferaby inert solvent at temperatures between about –20 °C and about 200 °C, preferably between –10 °C and 150 °C and especially between 0 °C or room temperature (25°) and 120°. In many cases, it is advantageous to combine one compound of formula III with one compound of formula IV at the lower end of the given temperature range, preferably between –20 °C and 75 °C, more preferred between 0 °C and 60 °C and especially between 10 °C and 40 °C, for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably between 65 °C and 180 °C, more preferred between 75 °C and 150 °C and especially between 80 °C and 120 °C, for example at about 80 °C, at about 90 °C or at about 100 °C. Proceeding in that manner can be advantageous in the case that pound of formula II is the compounds of formula II'. If the compound of formula II is not a compound of formula II', the reaction can be

regularly carried out without prolonged heating to higher temperatures. For example, it can preferably be carried out at a temperature between –10 °C and 60 °C, more preferably between –5 °C and 40 °C and even more preferably at about 0 °C or at about room temperature. This given temperature range is especially advantageous, if the compound of formula II is selected from compounds of formula IIa, IIb, IIc and especially is a compound of formula IIg or IIh.

The method for manufacture according to the invention is preferably carried out in the presence of an acid binding means, for example one or more bases. This is especially advantageous, if the compound of formula II is selected from compounds of formula IIa – IIc an even preferred if the compound is selected from the compounds of formula IIg or formula IIh.

Suitable acid binding means are known in the art. Preferred as acid binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), diaza bicyclo undecen (DBU), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as organic bases are pyridine and DIPEA. In many cases it is advantageous to employ two different organic bases and especially to use pyridine and DIPEA.

Reaction times are generally in the range between some minutes and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring.

Based on the reaction temperatures given above, suitable reaction times generally lie in the range 10 min and 36 hrs, preferably 30 min and 24 hrs and especially between 45 min and 18 hrs, for example about 1 h, about 2 hrs, about 4 hrs, about 6 or about 18 hrs.

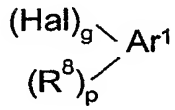
Preferably, the reaction of the compounds of the formula III with the compounds of the formula IV is carried out in the presence of a suitable solvent, that is preferably inert under the respective reaction conditions.. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are chlorinated hydrocarbons, especially dichloromethane, and amides, especially DMF.

In general, the compounds of formula III and/or formula IV are new. In any case, they can be prepared according to methods known in the art.

The compounds of formula III can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by one or more of the reaction routes given below:

Compounds of formula III can be readily obtained from synthesis sequence as given below:

The reaction of derivatives of formula (A)

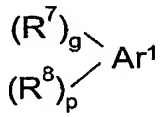


(A)

wherein Hal is Cl , Br or F and especially is F, and wherein g, R^8, p and Ar^1 are as defined above/below, with p compounds of formula (B)

(B)

wherein R^7 is as defined above/below and L^7 is preferably selected from H or a metal ion, if L^7 is bound to an oxygen atom of R^7 or to an nitrogen atom of R^7, or selected from carbon atom activating groups, if L^7 is bound to a carbon atom of R^7, leads to compounds of formula (C).



(C)

Suitable carbon atom activating groups for this type of reaction are known in the art. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Preferred metal ions are alkaline metal ions, of which Li, Na and/or K are especially preferred. Even more preferred as L^7 is H.

Accordingly, preferred compounds of formula (B) for the method for manufacture according to the invention are compounds that comprise a hydroxy-group, a primary amino group or a secondary amino group. Thus,

especially preferred are compounds of formula (B), that comprise an HO-, a H_2N-group, a HNR^{11}-group or a HNR^{12}-group, and especially compounds that comprise a terminal HO-, a H_2N-group, a HNR^{11}-group or a HNR^{12}-group, wherein R^{11} and R^{12} are as defined above/below.

This type of reaction is generally known as aromatic substitution. Suitable reaction conditions for the reaction of the compounds of formula (A) with the compounds of formula (B) are known in the art.

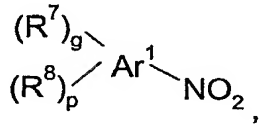
The compounds of formula (B) are preferably selected from HHet, HOHet, $HN(R^{11})$Het, $O(CR^5R^6)_k$Het, $HN(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $HO(CR^5R^6)_kNR^{11}R^{12}$, $HNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $HO(CR^5R^6)_kR^{13}$, $HNR^{11}(CR^5R^6)_kR^{13}$, $HO(CR^5R^6)_kOR^{13}$, $HNR^{11}(CR^5R^6)_kOR^{13}$, $HO(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $HNR^{11}(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $HO(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $HNR^{11}(CR^5R^6)_nNR^{12}(CR^5R^6)_kNR^{11}R^{12}$, $HO(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $HNR^{11}(CR^5R^6)_nO(CR^5R^6)_kOR^{12}$, $HO(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$ and $HNR^{12}(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, and the metal salts thereof.

If the compounds of formula (B) comprise more than one hydroxy group, primary amino group or secondary amino group (apart from the hydroxy group or amino group comprising L^7), it is advantageous to proceed the reaction using derivatives of compounds of formula (B), wherein the addotional hydroxy groups, primary amino groups or secondary amino groups are protected by so-called protecting groups, i.e. hydroxy protecting groups or amino protecting groups, respectively. Accordingly, if the compounds of formula I are to carry residues R^7 comprising one or more of R^{11}, R^{12}, R^{13} and R^{14} that are H, it is advantageous to employ compounds of formula (B), wherein these H-atoms are replaced by suitable protecting groups.

Suitable protecting groups are known in the art. For example, primary amino groups can be advantageously protected as phthalimides, secondary amino groups can be advantageously protected with the BOC-protecting group. Suitable methods and reaction conditions for producing protected derivatives of compounds of formula (B) and methods and reaction conditions for removing such protection groups from the accordingly obtained protected products are known in the art.

The compound of formula (C) then can be transferred into the compound of formula III by methods known in the art.

Advantageously, the compound of formula (C) then can be transferred into a compound of formula (D),



by a nitration reaction. Suitable methods and reaction conditions for nitration reactions are known in the art. Advantageously, the compounds of formula (D) can be obtained by reacting a compound of formula (C) with nitrating acid or a combination of concentrated sulfuric acid and potassium nitrate. If a combination of concentrated sulfuric acid and potassium nitrate is used, it can be advantageous to perform the reaction at a relatively low temperature, for example between -20 °C and + 50 °C, preferably between -10 °C and room temperature, more preferred between -5 °C and 0 °C.

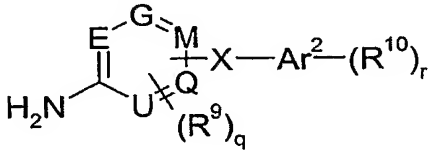
The compound of formula (D) then can be transferred into a compound of formula III, wherein L^3 and L^4 are hydrogen, preferably by a reduction reaction or hydrogenating reaction, preferably a hydrogenating reaction. Methods and reaction conditions for hydrogenating a NO_2-moiety into a NH_2-moiety are known in the art. In general, it is advantageous to carry out the

hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, for example Pd/C or Raney-nickel, preferably Raney-nickel. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. Preferred as solvent is a mixture of THF/methanol, preferably in about equal measures. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150°, preferably 0° and 50°. The obtained compound of formula III wherein L^3 and L^4 are hydrogen can optionally be isolated and/or purified and then optionally transferred into a compound of formula III wherein L^3 and L^4 are other than hydrogen, for example according to methods and reaction conditions as described herein.

Some of the starting materials of the formula V and/or the formula VI are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

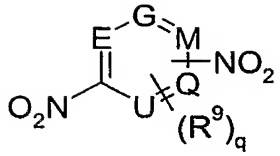
Generally, the compounds of formula IV can be obtained according to methods known in the art.

If the compound of formula IV is a compound according to formula IVa,



IVa

it can be readily obtained in an advantageous manner by reacting a compound of formula VIIa,



VIIa

wherein R^9 and q are as defined above/below,

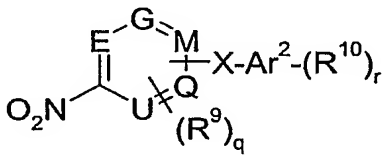
with a compound of formula VIII,

$$L^8\text{-}X\text{-}Ar^2\text{-}(R^{10})_r \qquad \text{VIII}$$

wherein L^8 is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminum ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and Ar^2, R^{10}, r and X are as defined above/below, and especially wherein X is $(CHR^{11})_h\text{-}Q\text{-}(CHR^{12})_i$, wherein R^{11}, h and R^{12} are defined above/below, i is 0 and Q is selected from a group consisting of O, S, N-R^{15}, $(CHR^{18}\text{-}O)_j$, $(CHR^{18}CHR^{19}\text{-}O)_j$, CH=N-O, CH=N-$NR^{15}$, SO_2NR^{15}, wherein R^{15}, R^{18} and R^{19} are as defined above/below;

optionally isolating the reaction product,

and transferring the obtained reaction product of formula IX

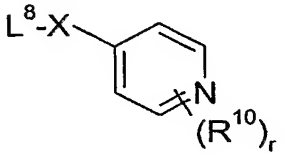


IX

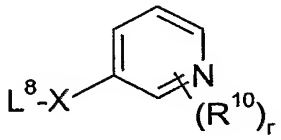
into a compound of formula IVa, preferably by hydrogenating the NO_2-moiety of the compound of formula IX into a NH_2-moiety. Methods and reaction conditions for hydrogenating said NO_2-moiety into a NH_2-moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction

in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150°, preferably 0° and 50°.

Ar^2 is preferably pyridinyl. Accordingly, the compound of formula VIII is preferably selected from the group consisting of formulae VIIIa and VIIIb,

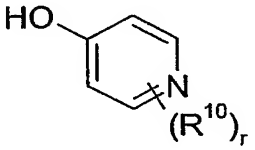


VIIIa

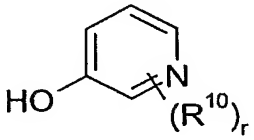


VIIIb

wherein L^8, X, R^{10} and r are as defined above, and especially preferred from the group consisting of formulae VIIIc and VIIId,



VIIIc



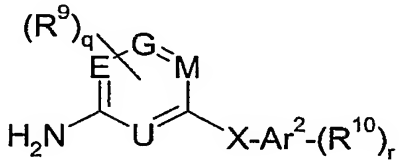
VIIId

wherein R^{10} and r are as defined above, or the alkaline metal salts and especially the sodium or potassium salts thereof.

Accordingly, in formulae IVa, VIII, VIIIa, VIIIb and IX, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

In the formulae VIII, VIIIa and VIIIb, L^8 is preferably H or selected from the group consisting of Na, K and Cs and especially preferred is H.

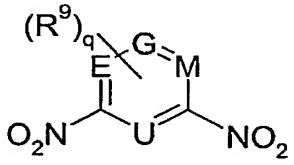
In general, this reaction is advantageous to produce compounds of formula IVaa,



IVaa

wherein R^9, q, X, Ar^2, R^{10} and r are as defined above/below.

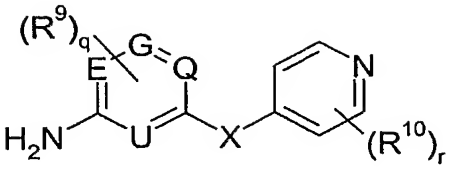
To obtain compounds of formula IVaa, it is reasonable to employ a compound of formula VII that is selected from the compounds of formula VIIa,



VIIa

and proceed the reaction as described above/below.

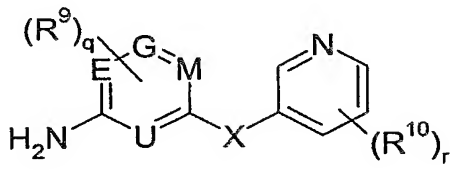
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIa, the reaction preferably leads to compounds of formula IVaaa,



IVaaa

wherein R^9, q, X, R^{10} and r are as defined above/below.

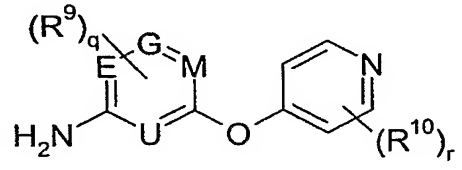
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIb, the reaction preferably leads to compounds of formula IVaab,



IVaab

wherein R^9, q, X, R^{10} and r are as defined above/below.

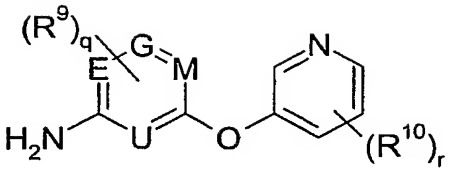
Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIIc, the reaction preferably leads to compounds of formula IVaac,



IVaac

wherein R^9, q, R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIa and a compound of formula VIIId, the reaction preferably leads to compounds of formula



IVaad

wherein R^9, q, R^{10} and r are as defined above/below.

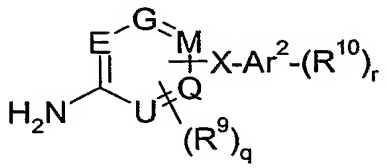
Some of the starting materials of the formula VII and/or the formula VIII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

The reaction between the compound of formula VII and VIII is preferably carried out in the temperature range between 0° and 250°, more preferred room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 30 min and 36 hrs, preferably 3 hrs and 24 hrs, more preferably 8 hrs and 20 hrs for example about 10 hrs, about 16 hrs or about 18 hrs.

The reaction can be carried out in the absence of solvent or preferably in the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high boiling aliphatic hydrocarbons, high boiling aromatic carbons, for example toluene, xylenes, high boiling chlorinated hydrocarbons, such as trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; high boiling ethers, such as ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents. Preferred are amides, especially dimethylformamide (DMF).

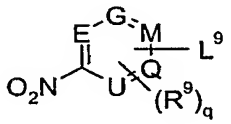
Preferably, the reaction is carried out in the presence of a base. Suitable bases are known in the art. Preferred bases are organic bases and especially inorganic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Preferred inorganic bases are K_2CO_3, Na_2CO_3, $MgCO_3$, $CaCO_3$, NaOH and KOH, especially preferred is K_2CO_3. Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction.

Alternatively, if the compound of formula IV is a compound according to formula IVb,



IVb

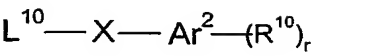
it can be readily obtained in an advantageous manner by reacting a compound of formula VIIb,



VIIb

wherein R^9 and q are as defined above/below and wherein L^9 is selected independently from the meanings given for L^1. Preferably, L^9 is halogen. More preferred, L^9 is selected from the group consisting of Cl, Br and I. Especially preferred, L^9 is Cl.

with a compound of formula VIIIb,

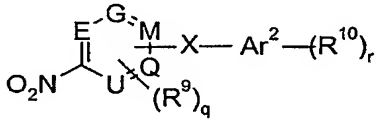


VIIIb

wherein L^{10} is H or a metal ion, preferably a metal ion, more preferred a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred; and Ar^2, R^{10}, r and X are as defined above/below, and especially wherein X is $(CHR^{11})_h$-Q-$(CHR^{12})_i$, CH=N-O, CH=N-NR^{15}, SO_2NR^{15}, wherein R^{15}, R^{18} and R^{19} are as defined above/below;

optionally isolating the reaction product,

and transferring the obtained reaction product of formula IXb

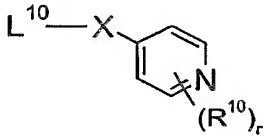


IXb

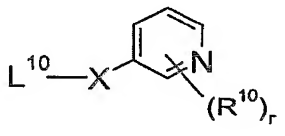
into a compound of formula IVa, preferably by hydrogenating the NO_2-moiety of the compound of formula IX into a NH_2-moiety. Methods and reaction conditions for hydrogenating said NO_2-moiety into a NH_2-moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol, ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between

normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between –20° and 150°, preferably 0° and 50°.

Ar^2 is preferably pyridinyl. Accordingly, the compound of formula VIIIb is preferably selected from the group consisting of formulae VIIIe and VIIIf,

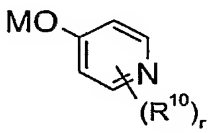


VIIIe

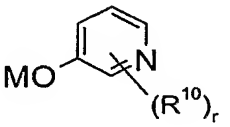


VIIIf

wherein L^{10}, X, R^{10} and r are as defined above, and especially preferred from the group consisting of formulae VIIIg and VIIIh,



VIIIg

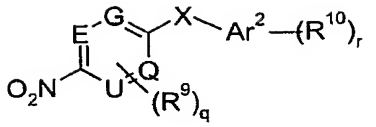


VIIIh

wherein R^{10} and r are as defined above, and wherein M is an alkaline metal ion and especially sodium or potassium, or the corresponding alcohols thereof.

Accordingly, in formulae IVb, VIIIb, VIIIe, VIIIf and IXb, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

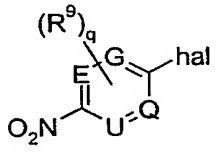
In general, this alternative reaction is advantageous to produce compounds of formula IVbb,



IVbb

wherein R^9, q, X, Ar^2, R^{10} and r are as defined above/below.

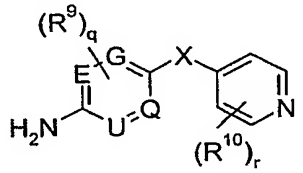
To obtain compounds of formula IVbb, it is reasonable to employ a compound of formula VIIb that is selected from the compounds of formula VIIbb,



VIIbb

wherein hal is as defined above/below and especially is Cl, and proceed the alternative reaction as described above/below.

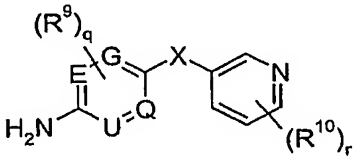
Accordingly, by starting from a compound a formula VIIbb and a compound of formula VIIe, the reaction preferably leads to compounds of formula IVbbe,



IVbbe

wherein R^9, q, X, R^{10} and r are as defined above/below.

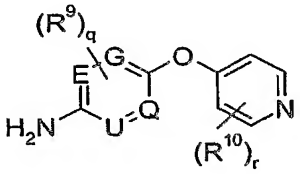
Accordingly, by starting from a compound of formula VIIbb and a compound of formula VIIIf, the reaction preferably leads to compounds of formula IVbbf,



IVbbf

wherein R^9, q, X, R^{10} and r are as defined above/below.

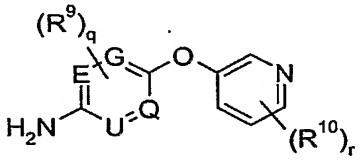
Accordingly, by starting from a compound of formula VIIbb and a compound of formula VIIIg, the reaction preferably leads to compounds of formula IVbbg,



IVbbg

wherein R^9, q, R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIb and a compound of formula VIIIh, the reaction preferably leads to compounds of formula IVbbh,



IVbbh

wherein R^9, q, R^{10} and r are as defined above/below.

Some of the starting materials of the formula VIIb and/or the formula VIIIb are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

The reaction between the compound of formula VIIb and VIIIb is preferably carried out in the temperature range between 0° and 250°, more preferred 50° and 220°, for example at about 90°, at about 120°, at about 160°, at about 180° or at about 200°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 10 min and 24 hrs, preferably 30 min and 12 hrs, more

preferably 1 h and 6 hrs for example about 1,5 hrs, about 3 hrs, about 4 hrs or about 5 hrs.

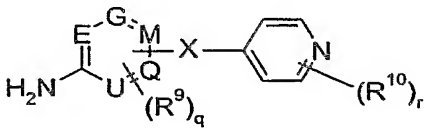
The reaction can be carried out in the absence or the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high boiling aliphatic hydrocarbons, aromatic carbons, for example toluene and xylenes, high boiling chlorinated hydrocarbons, such as dichloromethane, trichloromethane trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; ethers, such as diethylether, tert.-butyl methyl ether, ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); nitriles, such as acetonitrile, amides such as acetamide, diemthyacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents.

Preferably, the reaction is carried out in the presence of a catalyst. Suitable catalysts are known in the art. Preferred are catalytic active metals and especially copper.

Preferably, the reaction is carried out by heating up a reaction mixture comprising one compound of formula VIIb and one compound of formula VIIIb to a suitable reaction temperature, which preferably lies at the upper end of the given temperature ranges and more preferred is in the range between 150° and 200°, for example at about 180°, preferably in the presence of the suitable catalyst and especially in the presence of copper. Reaction times at this temperature are preferably as given above and especially in the range between 1 h and 5 hrs, for example about 3 hrs. Preferably, the reaction mixture is then allowed to cool down to a temperature in the lower range of the given temperature, more preferred to a temperature in the range between 50° and 150°, for example to about 90°.

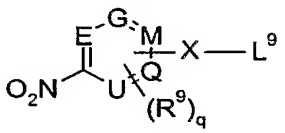
Preferably, a suitable solvent, preferably tert.-butyl methyl ether, is then added and the reaction mixture is preferably kept at about the same temperature for some more time, preferably for 30 min to 2 hrs and more preferred for about one hour.

If the compound IV is a compound according to formula IVc,



IVc

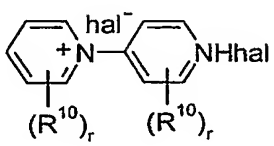
it can be readily obtained in an advantageous manner by reacting a compound of formula XI



XI

wherein L^9 is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and R^9, q and X are as defined above/below, and especially wherein X is $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein R^{11}, h and R^{12} are defined above/below, i is 0 and Q is selected from a group consisting of O, S, N-R^{15}, $(CHR^{18}$-O$)_j$, $(CHR^{18}CHR^{19}$-O$)_j$, CH=N-O, CH=N-NR^{15}, SO_2NR^{15}, wherein R^{15}, R^{18} and R^{19} are as defined above/below;

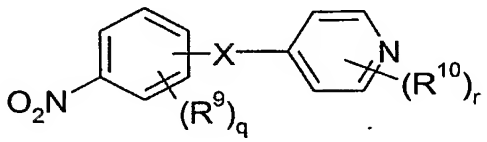
with a compound of formula XII,



XII

wherein hal is independently select selected from the group consisting of Cl, Br and I, the residues R^{10} are the same or different and have the meanings given above/below and preferably have both the same meaning, and the indices r are the same or different and have the meanings given above/below and preferably are the same,

optionally isolating the reaction product, and transferring the obtained reaction product of formula XIII



XIII

into a compound of formula IVc, preferably by hydrogenating the NO_2-moiety of the compound of formula XIII into a NH_2-moiety, for example as described above for the compound of formula IX.

In the compounds IVc, XII and XIII, r is preferably in each case identical and even more preferred in each case 0.

In formulae IVc, XI and XIII, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

In the formula XI, L^9 is preferably H or selected from the group consisting of Na and K, and especially preferred is H.

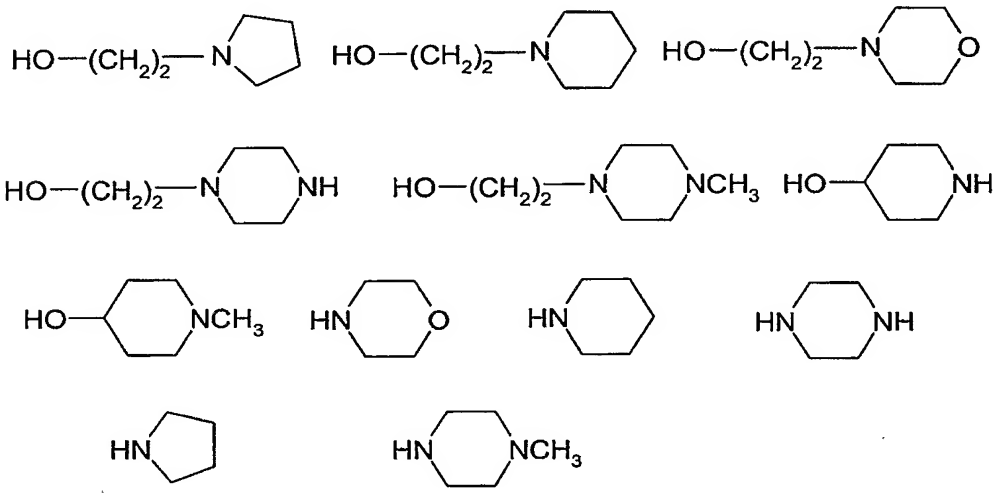
The reaction between the compound of formula XI and XII is preferably carried out in the temperature range between 0° and 250°, more preferred room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 30 min and 24 hrs, preferably one hour and 12 hrs, for example about 2 hrs,

about 3 hrs or about 6 hrs. The reaction can be carried out in the absence of solvent or in the presence of an solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art.

Some of the starting materials of the formula XI and/or the formula XII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues R^7, R^8, R^9 and/or R^{10} into one or more of the compounds described above, or, if the compound already comprises one or more residues R^7, R^8, R^9 and/or R^{10}, to introduce additional residues R^7, R^8, R^9 and/or R^{10} into said compound. The introduction of additional residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in compounds comprising Ar^1, wherein Ar^1 comprises one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons, preferably selected from the group consisting of $HO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_kR^{13}$, $HO(CH_2)_kOR^{11}$, $HO(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HO(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HO(CH_2)_nCOOR^{13}$, $HO(CH_2)_nS(O)_uR^{13}$, $HNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_kOR^{11}$, $HNR^{11}(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $HNR^{11}(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $HNR^{11}(CH_2)_nCOOR^{12}$ and $HNR^{11}(CH_2)_nS(O)_uR^{13}$, and the metal salts thereof, wherein R^{11}, R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. Even more preferred, the hydroxy, thio and/or amino substituted hydrocarbons are selected from the group consisting of NH_3, $HN(CH_3)_2$, NH_2CH_3, $HN(C_2H_5)_2$, $H_2NCH_2CH_2NH_2$, $HOCH_2CH_2NH_2$, $HOCH_2CH_2NHCH_3$, $HN(CH_3)CH_2CH_2NH_2$,

$HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2N(CH_3)_2$, $HN(CH_3)CH_2CH_2OCH_3$, $HOCH_2CH_2N(CH_3)_2$, $HOCH_2CH_2N(CH_2CH_3)_2$, $HSCH_3$, HSC_2H_5, and compounds of the formulae



or salts and especially metal salts thereof.

On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residues R^7, R^8, R^9 and/or R^{10} into residues R^7, R^8, R^9 and/or R^{10} other than the ones originally present. For example, CH_3-groups can be oxidized into aldehyde groups or carbonic acid groups, thio atom containing groups, for example S-alkyl or S-aryl groups, can be oxidized into SO_2-alkyl or SO_2-aryl groups, respectively, carboxylic acid groups can be derivatized to carboxylic acid ester groups or carboxylic acid amide groups and carboxylic acid ester groups or carboxylic acid amide groups can be hydrolysed into the corresponding carboxylic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as

Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding

metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds for the formula I and physiologically acceptable salts and solvates thereof as kinase inhibitors.

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non- chemical methods. In this cases, one or more compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, solvates of compounds of the formula I, salts of compounds of formula I, for the production of pharmaceutical compositions

and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds according to the invention into a dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingridients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients,

auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries, adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

tablets	mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression
capsules	mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules
semi-solids (ointments, gels, creams)	dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only)

suppositories (rectal and vaginal)	dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms
aerosols:	dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer

The invention thus relates to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates.

Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount of one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the skilled artisan or can be easily determined by standard methods known in the art. For example, the compounds according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors, especially in an analogous manner to the compounds described in WO 00/42012 (Bayer). Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg, more than 20 mg, more than 50 mg or more than 100 mg, and preferably less

than 1500 mg, more preferred less than 750 mg, even more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for example by the doctor or physician which advises or attends the therapeutic treatment.

However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is especially preferred.

These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsulees, powders, granules, syrups, juices or drops. Further examples for suitable dosage forms, which

are especially suitable for rectal administration are suppositories, further examples for suitable dosage forms, which are especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO_2 or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

In General, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of

factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumors, restenoses, diabetic retinopathy, macular degenerative disease or rheumatois arthritis.

Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc. Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfamicle, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16, carboplatinum, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

The compounds of the invention have been shown to have antiproliferative effect in an in vivo xenograft tumor model. The subject compounds are administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds are useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is preferably also used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted tissue,

while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

The compounds also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis, inflammation, endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of a variety of conditions where there is proliferation and/or migration of smooth

muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest include atherosclerosis, graft coronary vascular disease after transplantation, vein graft stenosis, peri-anastomatic prothetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

Diseases where there is hyperproliferation and tissue remodelling or repair or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to product a tumor neovasculature.

Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial, stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell urinary carcinoma etc.; neurological malignancies; e.g. neuroplastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are

primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential to metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamos cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph

node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocyctes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that bisarylurea derivatives according to invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the raf-kinase signaling pathway. Bisarylurea derivatives according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, bisarylurea derivatives according to invention show an effect, preferably a modulating

and especially an inhibiting effect which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferred in the nanomolar range.

In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably to one or more raf-kinases that preferably lies, determined as IC_{50}-value, in the range of 100 μmol or below, preferably 10 μmol or below, more preferably in the range of 3 μmol or below, even more preferably in the range of 1 μmol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined as IC_{50}-value, to one or more raf-kinases, preferably including A-raf, B-raf and c-raf1 or consisting of A-raf, B-raf and c-raf1 and more preferred including c-raf1 or consisting of c-raf1, in the range of 0.5 μmol or below and especially in the range of 0.1 μmol or below. In many cases an IC_{50}-value at the lower end of the given ranges is advantageous and in some cases it is highly desirable that the IC_{50}-value is as small as possible or the he IC_{50}-values are as small as possible, but in general IC_{50}-values that lie between the above given upper limits and a lower limit in the range of 0.0001 μmol, 0.001 μmol, 0.01 μmol or even above 0.1 μmol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary depending on the respective testing system or assay chosen.

Alternatively, the advantageous biological activity of the compounds according to the invention can easily be demonstrated in *in vitro* assays, such as *in vitro* proliferation assays or *in vitro* growth assays. Suitable *in vitro* assays are known in the art, for example from the literature cited herein and the references cited in the literature or can be performed as described below, or can be developed and/or performed in an analogous manner thereof.

As an example for an *in vitro* growth assay, human tumor cell lines, for example HCT116, DLD-1 or MiaPaCa, containing mutated K-ras genes can be used in standard proliferation assays, for example for anchorage dependent growth on plastic or anchorage independent growth in soft agar. Human tumor cell lines are commercially available, for example from ATCC (Rockville MD), and can be cultured according to methods known in the art, for example in RPMI with 10% heat inactivated fetal bovine serum and 200 mM glutamine. Cell culture media, fetal bovine serum and additives are commercially available, for example from Invitrogen/Gibco/BRL (Karlsruhe, Germany) and/or QRH Biosciences (Lenexa, KS). In a standard proliferation assay for anchorage dependent growth, 3 X 10^3 cells can be seeded into 96-well tissue culture plates and allowed to attach, for example overnight at 37 °C in a 5% CO_2 incubator. Compounds can be titrated in media in dilution series and added to 96 well cell cultures. Cells are allowed to grow, for example for 1 to 5 days, typically with a feeding of fresh compound containing media at about half of the time of the growing period, for example on day 3, if the cells are allowed to grow 5 days. Proliferation can be monitored by methods known in the art, such as measuring metabolic activity, for example with standard XTT colorimetric assay (Boehringer Mannheim) measured by standard ELISA plate reader at OD 490/560, by measuring ^{3}H-thymidine incorporation into DNA following an 8 h culture with 1μCu ^{3}H-thymidine, harvesting the cells onto glass fiber mats using a cell harvester and measuring ^{3}H-thymidine incorporation by liquid scintillation counting, or by staining techniques, such as crystal violet staining. Other suitable cellular assay systems are known in the art.

Alternatively, for anchorage independent cell growth, cells can be plated at 1 x 10^3 to 3 x 10^3 in 0.4% Seaplaque agarose in RPMI complete media, overlaying a bottom layer containing only 0.64% agar in RPMI complete media, for example in 24-well tissue culture plates. Complete media plus dilution series of compounds can be added to wells and incubated, for example at 37 °C in a 5% CO_2 incubator for a sufficient time, for example 10-

14 days, preferably with repeated feedings of fresh media containing compound, typically at 3-4 day intervals. Colony formation and total cell mass can be monitored, average colony size and number of colonies can be quantitated according to methods known in the art, for example using image capture technology and image analysis software. Image capture technology and image analysis software, such as Image Pro Plus or media Cybernetics.

As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling pathways, bisarylurea derivatives are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

The compounds according to the invention are preferably kinase modulators and more preferably kinase inhibitors. According to the invention, kinases include, but are not limited to one or more Raf-kinases, one or more Tie-kinases, one or more VEGFR-kinases, one or more PDGFR-kinases, p38-kinase and/or SAPK2alpha.

Raf-kinases in this respect are respect preferably include or consist of A-Raf, B-Raf and c-Raf1.

Tie-kinases in this respect preferably include or consist of Tie-2 kinase.

VEGFR-kinases in this respect preferably include or consist of VEGFR-2 kinase.

Due to the kinase modulating or inhibting properties of the compounds according to the invention, the compounds according to the invention preferably interact with one or more signalling pathways which are preferably cell signalling pathways, preferably by downregulating or inhibiting said signaling pathways. Examples for such signalling pathways include, but are not limited to the raf-kinase pathway, the Tie-kinase pathway, the VEGFR-

kinase pathway, the PDGFR-kinase pathway, the p38-kinase pathway, the SAPK2alpha pathway and/or the Ras-pathway.

Modulation of the raf-kinase pathway plays an important role in various cancerous and noncancerous disorders, preferably cancerous disorders, such as dermatological tumors, haematological tumors, sarcomas, squamous cell cancer, gastric cancer, head cancer, neck cancer, oesophageal cancer, lymphoma, ovary cancer, uterine cancer and/or prostate cancer. Modulation of the raf-kinase pathway plays a even more important role in various cancer types which show a constitutive activation of the raf-kinase dependent signalling pathway, such as melanoma, colorectal cancer, lung cancer, brain cancer, pancreatic cancer, breast cancer, gynaecological cancer, ovarian cancar, thyroid cancer, chronic leukaemia and acute leukaemia, bladder cancer, hepatic cancer and/or renal cancer. Modulation of the raf-kinase pathway plays also an important role in infection diseases, preferably the infection diseases as mentioned above/below and especially in Helicobacter pylori infections, such as Helicobacter pylori infection during peptic ulcer disease.

One or more of the signalling pathways mentioned above/below and especially the VEGFR-kinase pathway plays an important role in angiogenesis. Accordingly, due to the kinase modulating or inhibting properties of the compounds according to the invention, the compounds according to the invention are suitable for the prophylaxis and/or treatment of pathological processes or disorders caused, mediated and/or propagated by angiogenesis, for example by inducing anti-angiogenesis. Pathological processes or disorders caused, mediated and/or propagated by angiogenesis include, but are not limited to tumors, especially solid tumors, arthritis, especially heumatic or rheumatoid arthritis, diabetic retinopathy, psoriasis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic

disorders, inflammation and neurodegenerative diseases, and especially solid tumors, rheumatic arthritis, diabetic retinopathy and psoriasis.

Modulation of the p38-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis, and especially noncancerous disorders such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease.

Modulation of the PDGF-signalling pathway plays an important role in various cancerous and although in various noncancerous disorders, such as rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma and/or inflammatory bowel disease, and especially noncancerous disorders such as fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and/or angiogenesis.

Subject of the present invention are therefore bisarylurea derivatives according to the invention as promoters or inhibitors, preferably as inhibitors, of the signaling pathways described herein. Preferred subject of the invention are therefore bisarylurea derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase pathway. More preferred subject of the invention are therefore bisarylurea derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase. Even more preferred subject of the invention are bisarylurea derivatives according to invention as promoters or inhibitors, preferably as inhibitors of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Especially preferred subject of the invention are bisarylurea derivatives according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1.

Thus, subject of the present invention are bisarylurea derivatives according to the invention as medicaments. Subject of the present invention are bisarylurea derivatives according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more bisarylurea derivatives according to the invention as a pharmaceutical. Further subject of the present invention is the use of one or more bisarylurea derivatives according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/ or propagated by signalling pathways discussed herein, even more preferred disorders that are caused, mediated and/or propagated by raf-kinases and especially disorders that are caused, mediated and/or propagated by raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, psioarsis, arthritis, inflammation, endometriosis, scarring, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which arthritis, inflammation, immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are bisarylurea derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis of said disorders and the use of bisarylurea derivatives according to the invention for

the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more bisarylurea derivatives according to the invention to a patient in need of such an administration. Subject of the present invention therefore are bisarylurea derivatives according to the invention as medicaments and/or medicament active ingredients in the treatment and/or the prophylaxis said disorders and the use of bisarylurea derivatives according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more bisarylurea derivatives according to the invention to a patient in need of such an administration.

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more bisarylurea derivatives according to the invention. Subject of the present invention are especially pharmaceutical compositions that contain one or more bisarylurea derivatives according to the invention and one or more additional compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more bisarylurea derivatives according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers, excipients, auxiliaries, adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, the use of the compounds according to the invention in the treatment of Hyperproliferative disorders is a subject of the instant invention.

Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention.

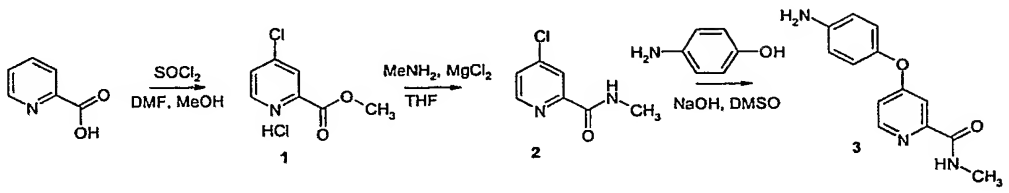
Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated $NaHCO_3$ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to bisarylurea derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

Examples

Experimental part

i) Synthesis of the pyridine units



a) 1) 750 ml of thionyl chloride are heated to 45°C under an N_2 atmosphere, and 23 ml of DMF are added dropwise. 250 g (2.031 mol) of pyridine-2-carboxylic acid are subsequently added in portions, and the reaction mixture is stirred at 45°C for a further 15 minutes and at 80°C for 24 hours. The yellow suspension is evaporated, and the residue is entrained a number of times with toluene. The oily residue is dissolved in 180 ml of toluene, the solution is cooled to 0°C, and 110 ml of methanol are added dropwise. The suspension is stirred for a further hour, and the precipitated solid is filtered off with suction and rinsed with toluene. The resultant crude product is recrystallised a number of times from acetone and dried in a vacuum drying cabinet.
Yield: 140 g (33%) of **1**, pale crystals

b) 2) 140 g (0.673 mol) of **1** are stirred with 32 g (0.336 mol) of magnesium chloride and 2 l of THF at room temperature. After 5 minutes, 1.36 l (2.369 mol) of methylamine are added dropwise over the course of 20 minutes. The suspension is stirred at room temperature for a further 16 hours. 1.3 l of water and 680 ml of 1N HCl solution are added to the reaction mixture, and the mixture is extracted with ethyl acetate (3 x 1 l). The combined organic phases are washed with a saturated NaCl solution, dried using sodium sulfate, filtered and evaporated. The crude product is

taken up in 300 ml of ethyl acetate and extracted with 200 ml of 1N HCl solution. The aqueous phase is adjusted to pH 9 using a 25% NH_4OH solution and extracted with ethyl acetate (2 x 400 ml). The organic phase is dried using sodium sulfate, filtered and evaporated.

Yield: 93 g (81%) of **2**, brown oil

c) 3a) 50 g (0.293 mol) of **2** and 32.6 g (0.293 mol) of 4-aminophenol are dissolved in DMSO, and 29.3 g (0.733 mol) of sodium hydroxide are slowly added. The solution is then heated at 100°C overnight. After a further 29.3 g (0.733 mol) of sodium hydroxide had been added, the reaction mixture is again stirred at 100°C overnight. The reaction mixture is cooled to room temperature, ice-water is added, and the mixture is extracted a number of times with diethyl ether. The combined organic phases are dried using sodium sulfate, filtered and evaporated.

Yield: 36 g (51%) of **3a**, brown oil

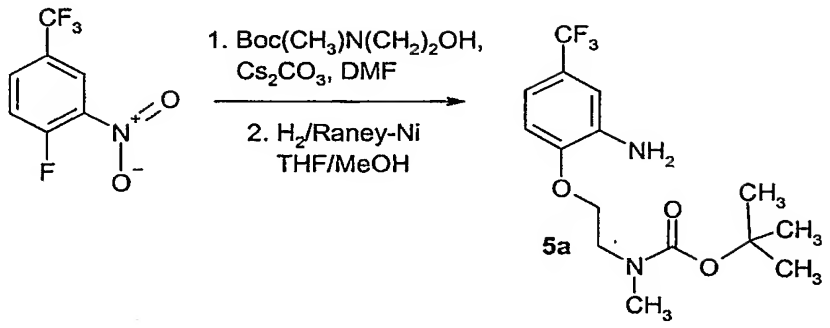
3b) 2.8 g (16.41 mmol) **2** and 4.6 g (32.83 mmol) 3-nitrophenol are stirred at 150 °C overnight. The reaction mixture is cooled to room temperature, treated with ethyl acetate and 2N NaOH-solution. The organic phase is separated and the water phase is extracted 2x with ethylacetate. The combined organic phases are washed 2x with brine, dried over sodium sulfate, filtered and evaporated. The residue is put on silica gel and purified by column chromatography (eluent : n-heptane/ethylacetate).

d) Yield: 2.88 g (62 %), pale yellow crystals

e) The accordingly obtained product is hydrogenated with H_2/Raney-Ni in THF/methanol at room temperature. The reaction mixture is filtered through a Seitz-filtre and rinsed with MeOH. The filtrate is concentrated, taken up in dichloromethane, dried over sodium sulfate, filtered and evaporated.

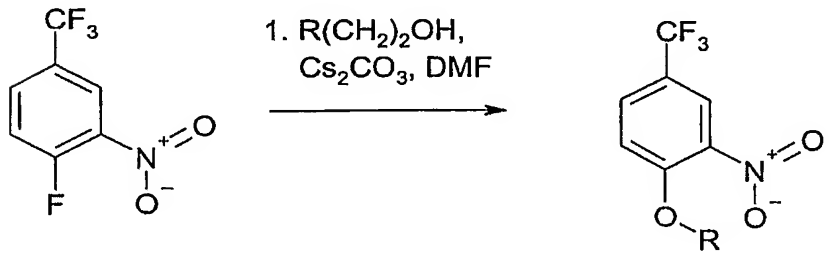
f) Yield: 2.29 g (92 %) **3b**, brown oil

ii) Synthesis of the anilines



3 ml (21 mmol) 4-Fluoro-3-nitrobenzotrifluoride are dissolved in dimethylformamide (DMF), treated with 4.4 g (25 mmol) N-Boc-N-methylaminoethanol and 20.7 g (63 mmol) cesium carbonate and stirred at 55 °C overnight. The reaction mixture is filtered by suction and the filtrate is evaporated. The residue is taken up in ethyl acetate and washed several times with water. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness.
Yield: 6.9 g (90 %), brown oil which crystallises upon standing

The accordingly obtained nitro compound is hydrogenated with H_2/Raney-Ni in THF/methanol - 1/1 at room temperature within 1 h. The catalyst is removed by filtration and the filtrate is evaporated to dryness. The crystalline residue is digested with petrol ether and filtered by suction.
Yield: 4.66 g (72 %) **5a**, pale grey crystals



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5 mmol 4-Fluoro-3-nitrobenzotrifluoride, 5-7.5 mmol substituted 2-amino ethanol ($R(CH_2)_2OH$) and 11.5-12.5 mmol cesiumcarbonate are dissolved in DMF and stirred at room temperature or 50 - 80 °C until a full conversion is achieved. Depending from from the reaction route chosen, the reaction mixture is worked up according the following variants:

Variant A: the reaction mixture is filtered and the residue rinsed with ethyl acetate. The filtrate is diluted with ethyl acetate, washed 3x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The residue is purified by column chromatography (silica gel, eluent: DCM/MeOH 0-5% in 45min).

Variant B: the reaction mixture is filtered by suction and rinsed with little DMF. The filtrate is evaporated. The oily residue is taken up in 100 ml water and extracted 3x with acyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4, and evaporated. The residue is purified by column chromatography (silica gel, eluent: DCM/MeOH 0-5% in 45min).

Variant C: the reaction mixture is filtered by suction and rinsed with little DMF. The filtrate is evaporated. The all the residue is taken up in 100 ml water and extracted 3x with acyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4, and evaporated.

Substituents, reaction conditions and yields:

4b: R = $(CH_2)_2N(CH_2)_4$; 50 °C, over night, working up procedure: A, 71 %, yellow oil

4c: R = $(CH_2)_2N(CH_3)_2$; room temperature, over night, working up procedure: A, 85 %, yellow oil

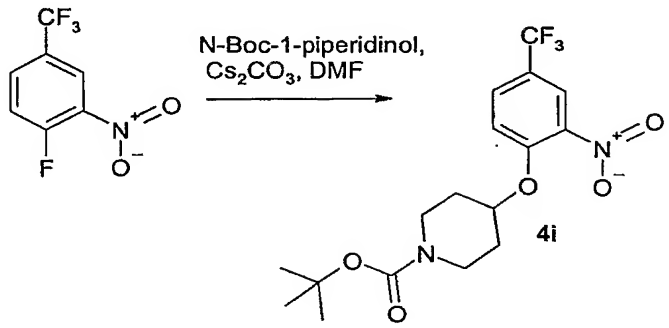
4d: R = $(CH_2)_2N(C_2H_5)_2$; 70 °C, 2 h, working up procedure: A, 90 %, yellow oil

4e: R = $(CH_2)_2N(CH_2)_2O(CH_2)_2$; 50 °C, over night, working up procedure: B, 74 %, red-brown oil

4f: R = $(CH_2)_2N(CH_2)_2NBoc(CH_2)_2$; 50 °C, over night, working up procedure: A, 84 %, yellow oil

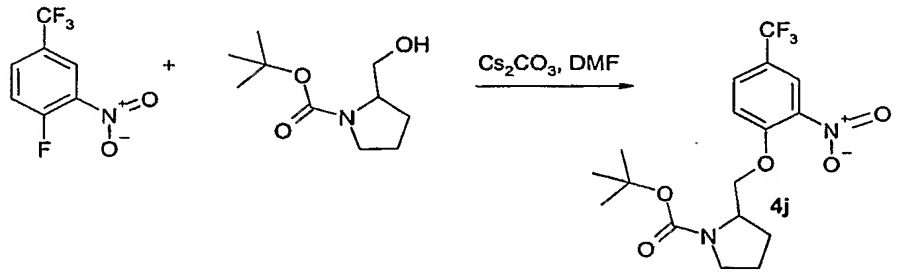
4g: R = $(CH_2)_2NBocCH(CH_3)_2$; 80 °C, 4 h, working up procedure: C, 65 %, yellow oil

4h: R = $CH_2C(CH_3)_2NBoc$; 50 °C, 2.5 h, working up procedure: B, 78 %, yellow crystals



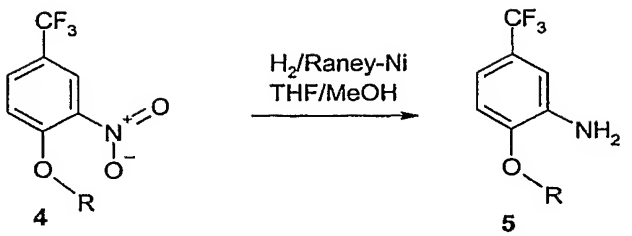
Manufacture according to the general working procedure for the compounds **4b-4h**:

4i: 80 °C, 5 h, working up procedure: A, 62 %, yellow oil



Manufacture according to the general working procedure for the compounds **4b-4h.**

4j: 50 °C, 3 h, working up procedure: C, 92 %, yellow oil



The thus obtained nitro compounds **4b-j** are hydrogenated in THF with H_2 and Pd/C (5%) or THF/Methanol - 1/1 with H_2 and Raney-Ni (5%) at room temperature until a full conversion is achieved. The catalyst is removed by filtration and the filtrate is evaporated to dryness.

Substituents, reaction conditions and yields:

5b: R = $(CH_2)_2N(CH_2)_4$; Pd/C, 18 h, 99.5 %, yellow oil, crystallises upon standing

5c: R = $(CH_2)_2N(CH_3)_2$; Pd/C, 23 h, 98 %, yellow crystals

5d: R = $(CH_2)_2N(C_2H_5)_2$; Pd/C, 21 h, 77 %, brown oil

5e: R = $(CH_2)_2N(CH_2)_2O(CH_2)_2$; Pd/C, 21 h, 99 %, beige solid

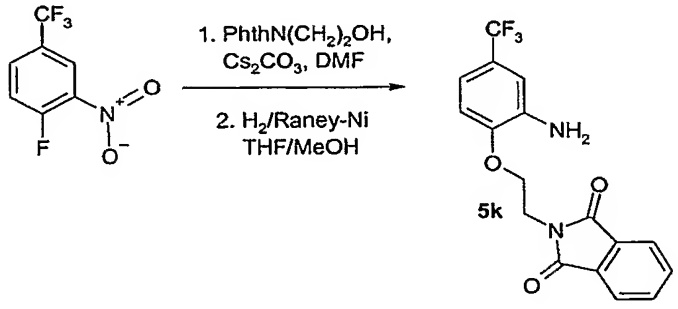
5f: R = $(CH_2)_2N(CH_2)_2NBoc(CH_2)_2$; Raney-Ni, 21 h, 92 %, brown oil

5g: R = $(CH_2)_2NBocCH(CH_3)_2$; Pd/C, 16 h, 98 %, brown oil

5h: R = $CH_2C(CH_3)_2NBoc$; Pd/C, 42 h, 99 %, beige crystals

5i: from **4i**, Raney-Ni, 23 h, 95 %, grey solid

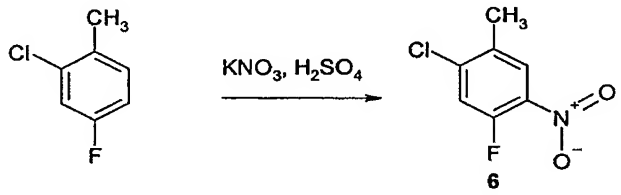
5j: from **4j**, Pd/C, 18 h, 97 %, colourless oil



0.67 ml (4.6 mmol) 4-Fluoro-3-nitrobenzotrifluoride are dissolved in DMF, treated with 1.08 g (5.6 mmol) N-(2-Hydroxyethyl)phthalimide and 3.82 g

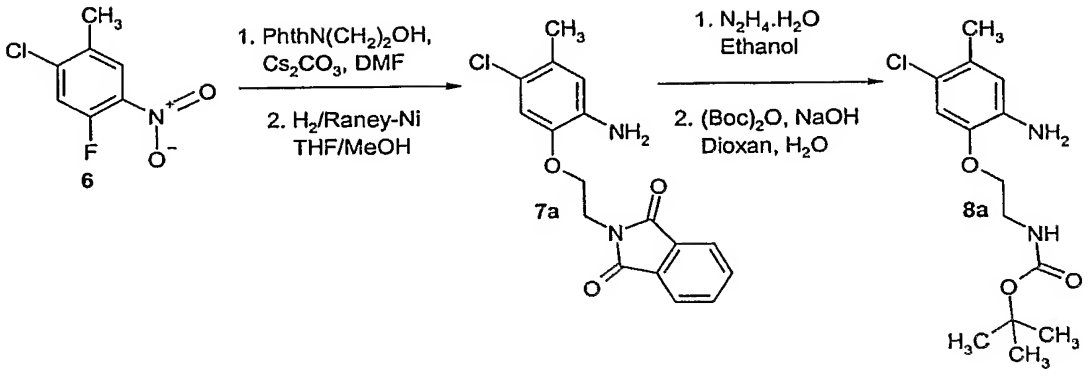
(11.6 mmol) cesium carbonate and stirred for 5.5 h at 50 °C. The reaction mixture is filtered by suction and the filtrate is evaporated to dryness. The residue is taken up in ethyl acetate and washed several times with water. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. Yield: 1.15 g (61 %) **4k**, yellow solid

1.1 g (2.7 mmol) of the accordingly obtained nitro compound is hydrogenated with H_2/Raney-Ni in THF/methanol - 1/1 at room temperature overnight. The catalyst is removed by filtration and the filtrate is evaporated to dryness. The crystalline residue is digested with methanol and filtered by suction. Yield: 1.04 g (93 %) **5k**, yellow solid



6

55 g (380 mmol) 2-Chloro-4-fluoro toluene are dissolved in 500 ml concentrated sulfuric acid and cooled to -5 - 0 °C in an ice bath. To this solution, 50.6 g (500 mmol) potassium nitrate are added in several portions within 1h. The reaction mixture is warmed up to room temperature overnight and then poured onto ice. The yellow suspension is extracted 3x with 1l tert.-Butyl-methylether each time and the combined organic phases are washed neutral with $NaHCO_3$-solution. The organic phase is stirred with Na_2SO_4 and 10 g charcoal, filtered and the filtrate is evaporated to dryness. Yield: 60 g (81 %) **6**, yellow oil, which crystallises in the refrigerator



8 g (42.2 mmol) 2-Chloro-4-fluoro-5-nitrotoluene are dissolved in DMF, treated with 8.07 g (42.2 mmol) N-(2-Hydroxyethyl)phthalimide and 27.5 g (84.4 mmol) cesium carbonate and stirred at 80 °C for 5.5 h. The reaction mixture is cooled to room temperature, filtered by suction and washed with DMF. The filtrate is evaporated to dryness. The residue is taken up in ethyl acetate, washed 3x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The residue is digested with diethylether/MTB-ether (1:1), filtered by suction, washed with ethyl acetate/MTB-ether (1:1) and dried in vacuo.

Yield: 3.65 g (24 %), pale yellow solid

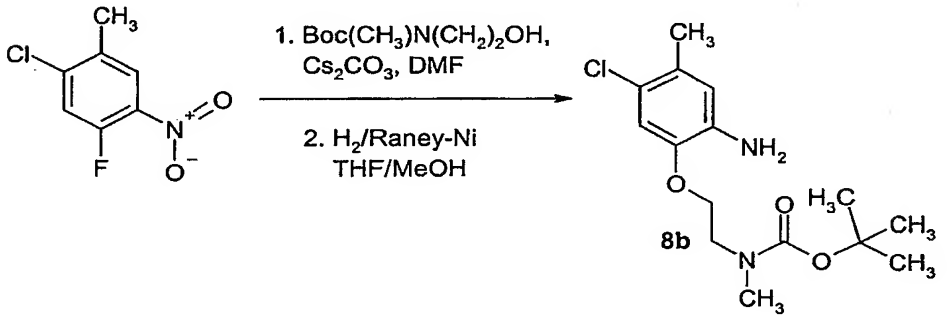
3.65 g (10.1 mmol) of the accordingly obtained nitro compound is hydrogenated with H_2/Raney-Ni in THF/methanol - 1/1 at room temperature overnight. The catalyst is removed by filtration and the filtrate is evaporated to dryness.

Yield: 3.09 g (92 %) **7a**, pale grey solid

0.7 g (2.05 mmol) **7a** are suspended in 30 ml ethanol under stirring, treated with 114 µl (2.36 mmol) hydrazine hydrate and the reaction mixture is then heated 2 days to reflux. The formed precipitate is filtered off by suction and washed with ethanol. The combined filtrates are evaporated to dryness, the residue is taken up in ethyl acetate and extracted 2x with 1N HCl-solution. The combined water phases are made alkaline with 2N NaOH-solution and

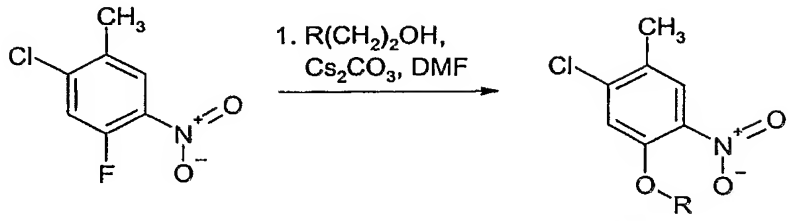
extracted 3x with ethyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4 filtered and evaporated.
Yield: 0.42 g (95 %), pale brown oil

0.34 g (1.58 mmol) of the accordingly obtained amine are dissolved in 3.5 ml dioxane, 1.7 ml 1N NaOH and 1.7 ml water by stirring at room temperature. The solution is cooled to 0 °C and at this temperature treated slowly with a solution of 379 mg (1.74 mmol) di-tert.-butyl dicarbonate in 1 ml dioxane. The reaction mixture is slowly warmed to room temperature, stirred for 18 h and then evaporated. The residue is taken up in 20 ml ethyl acetate, washed 2x with 15 ml water each time and 1x with brine, dried over Na_2SO_4, filtered and evaporated.
Yield: 0.47 g (99 %) **8a**, beige solid



0.55 g (2.81 mmol) 2-Chloro-4-fluoro-5-nitrotoluene are dissolved in DMF, treated with 0.59 g (3.38 mmol) N-Boc-N-methylaminoethanol and 2.11 g (6.47 mmol) cesium carbonate and stirred at 50 °C overnight. The reaction mixture is filtered by suction and the filtrate is evaporated. The residue is taken up in ethyl acetate, washed several times with water, dried over Na_2SO_4, filtered and then evaporated to dryness.
Yield: 0.94 g (97 %) **7b**, brown oil
The accordingly obtained nitro compound is hydrogenated with H_2/Raney-Ni in THF at room temperature. The catalyst is removed by filtration and the filtrate is evaporated to dryness.

Yield: 0.83 g (96 %) **8b**, brown oil



7

5 mmol 2-Chloro-4-fluoro-5-nitrotoluene, 5-7.5 mmol substituted 2-amino ethanol ($R(CH_2)_2OH$) and 11.5-12.5 mmol cesiumcarbonate are dissolved in DMF and stirred at room temperature or 50 - 80 °C until a full conversion is achieved. Depending from from the reaction route chosen, the reaction mixture is worked up according the following variants:

Variant A: the reaction mixture is filtered and the residue rinsed with ethyl acetate. The filtrate is diluted with ethyl acetate, washed 3x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The residue is purified by column chromatography (silica gel, eluent: DCM/MeOH 0-5% in 45min).

Variant B: the reaction mixture is filtered by suction and rinsed with little DMF. The filtrate is evaporated. The oily residue is taken up in 100 ml water and extracted 3x with acyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4, and evaporated. The residue is purified by column chromatography (silica gel, eluent: DCM/MeOH 0-5% in 45min).

Variant C: the reaction mixture is filtered by suction and rinsed with little DMF. The filtrate is evaporated. The oily residue is taken up in 100 ml water and extracted 3x with acyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4, and evaporated.

Substituents, reaction conditions and yields:

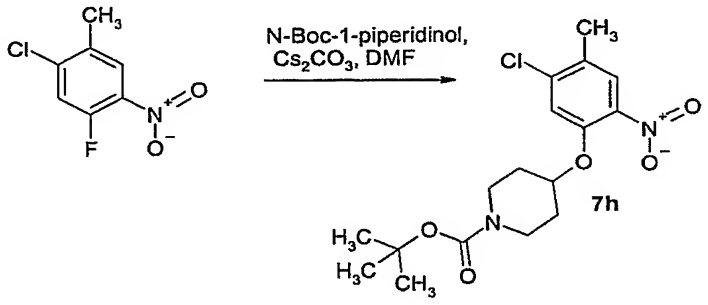
7c: R = $(CH_2)_2N(CH_2)_4$; 50 °C, over night, working up procedure: C, 87 %, red-brown solid

7d: R = $(CH_2)_2N(CH_3)_2$; 50 °C, overnight, working up procedure: C, 93 %, brown oil

7e: R = $(CH_2)_2N(C_2H_5)_2$; 50 °C, overnight, working up procedure: B, 72 %, yellow oil

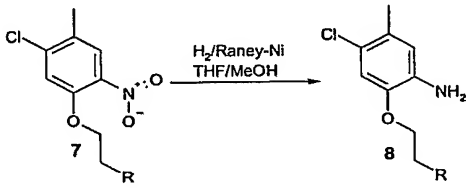
7f: R = $(CH_2)_2N(CH_2)_2O(CH_2)_2$; 50 °C, overnight, working up procedure: B, 71 %, brown crystals

7g: R = $(CH_2)_2N(CH_2)_2NBoc(CH_2)_2$; 50 °C, overnight, working up procedure: C, 90 %, brown oil



Manufacture according to the general working procedure for the compounds **7c-7g**.

7h: 50 °C, overnight, working up procedure: C, 99 %, brown oil



The accordingly obtained nitro compounds **7c-h** are hydrogenated with H_2/Raney-Ni in THF at room temperature until a full conversion is achieved. The catalyst is removed by filtration and the filtrate is evaporated to dryness. The crystalline residue is digested with petrol ether and filtered by suction.

Substituents, reaction conditions and yields:

8c: R = $N(CH_2)_4$; 23 h, 95 %, brown crystals

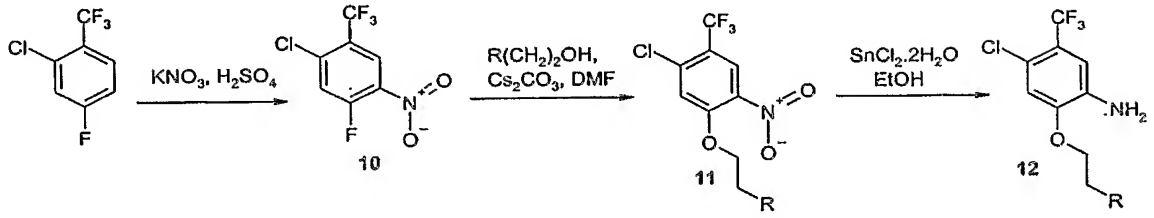
8d: R = $N(CH_3)_2$; 17 h, 79 %, brown crystals

8e: R = $N(C_2H_5)_2$; 18.5 h, 99 %, brown oil

8f: R = $N(CH_2)_2O(CH_2)_2$; 23 h, 80 %, yellow solid

8g: R = $N(CH_2)_2NBoc(CH_2)_2$; 17 h, 99 %, brown crystals

8h: from 7h, 45 h, 99 %, brown oil



46 g (227 mmol) 2-Chloro-4-fluoro-benzotrifluoride are dissolved in 460 ml concentrated sulfuric acid and cooled to -5 - 0 °C in an ice bath. To this solution, 27.55 g (272.5 mmol) potassium nitrate are added in several portions within 1h. After 30 min the reaction mixture is warmed to room temperature and stirred for 22 h. The reaction mixture is poured onto ice and extracted 3x with ethyl acetate. The combined organic phases are washed 1x with saturated $NaHCO_3$-solution and 1x with brine, dried over, Na_2SO_4, filtered and evaporated. The residue crystallises upon standing overnight. The crystals were digested with little petrol ether, filtered by suction and dried in vacuo.

Yield: 48.8 g (88 %) **10**, pale yellow crystals

10 mmol 5-Chloro-4-fluoro-3-nitrobenzotrifluoride are dissolved in DMF together with 12-20 mmol substituted 2-aminoethanol ($R(CH_2)_2OH$) and 23-25 mmol cesium carbonate in DMF and stirred until a full conversion is achieved. Depending on the course of the reaction the reaction mixture is worked up according to the following variants:

Variant A: the reaction mixture is filtered and the residue washed with dichloromethane. The filtrate is diluted with dichloromethane, washed 3x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The residue is purified by column chromatography (120 g silica gel, eluent:

DCM/MeOH 0-5% in 45min). The accordingly isolated product is taken up again in dichloromethane, washed 1x with 1N NaOH, 2x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated.

Variant B: the reaction mixture is filtered by suction and washed with DMF. The filtrate is evaporated. The oily residue is taken up in 40 ml water and extracted 4x with ethyl acetate. The combined organic phases are washed 2x with 1N NaOH and with water, dried over Na_2SO_4, filtered and evaporated.

Variant C: the reaction mixture is filtered by suction and washed with DMF. The filtrate is evaporated. The oily residue is taken up in 100 ml water and extracted 3x with ethyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The accordingly obtained pale brown solid is digested with dichloromethane and the filtrate is concentrated.

Variant D: the reaction mixture is filtered by suction, the filtrate diluted with ethyl acetate and extracted 2x with water. The organic phases dried over Na_2SO_4, filtered and evaporated. The oily residue is taken up in dichloromethane, washed 1x with 1N NaOH and then 1x with water, dried over Na_2SO_4, filtered and evaporated.

Variant E: the reaction mixture is filtered by suction and the filtrate is evaporated. The oily residue is digested with dichloromethane. The solid is filtered off by suction and washed with dichloromethane. The filtrate is washed 1x with 1N NaOH and 2x with water, dried over Na_2SO_4, filtered and evaporated.

Substituents, reaction conditions and yields:

11a: R = $N(CH_3)_2$; room temperature, 3 h, working up procedure: A, 54 %, yellow oil, crystallises upon standing

11b: R = $N(C_2H_5)_2$; 50 °C, 2 h, working up procedure: B, 67 %, pale brown oil

11c: R = $N(CH_2)_4$; 50 °C, 1 h, working up procedure: C, 62 %, yellow solid

11d: R = $N(CH_2)_2O(CH_2)_2$; 50 °C, 1 h, working up procedure: C, 62 %, yellow solid

11e: R = $N(CH_2)_2NBoc(CH_2)_2$; room temperature, 15 h, working up procedure: D, 92 %, brown oil

11f: R = $N(CH_3)Boc$; 50 °C, 2.5 h, working up procedure: E, 93 %, yellow oil

10 mmol of the nitro compounds **11a-f** are stirred in Ethanol mit 40-50 mmol tin(II)chloride-dihydrate at room temperature or at 70 °C until a full conversion is achieved. The reaction mixture is made alkaline with $NaHCO_3$-solution. The formed precipitate is filtered off by suction over kieselguhr and the precipitate is washed with ethanol and ethyl acetate. The filtrate is concentrated with a Rotavapor until a water phase is obtained, which is extracted 3x with ethyl acetate. The combined organic phases are washed 1x with brine, dried over Na_2SO_4, filtered and evaporated.

Substituents, reaction conditions and yields:

12a: R = $N(CH_3)_2$; 70 °C, 3 h, 84 %, yellow oil, crystallises upon standing

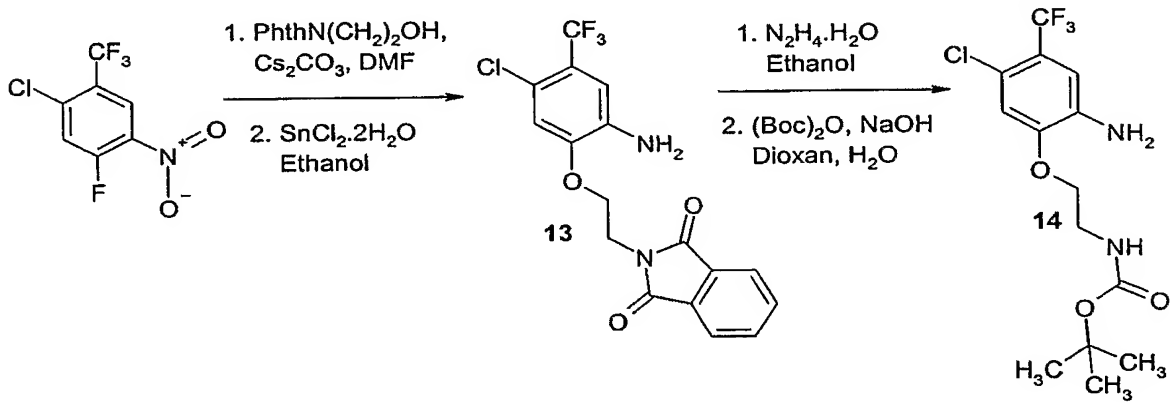
12b: R = $N(C_2H_5)_2$; 70 °C, 1.5 h, 75 %, pale brown oil

12c: R = $N(CH_2)_4$; 70 °C, 1 h, 58 %, brown oil

12d: R = $N(CH_2)_2O(CH_2)_2$; 70 °C, 1.5 h, 56 %, pale brown oil

12e: R = $N(CH_2)_2NBoc(CH_2)_2$; room temperature, 1.5 h, 41 %, brown oil

12f: R = $N(CH_3)Boc$; room temperature, 1.5 h, 53 %, brown oil



8 g (32.85 mmol) 5-Chloro-4-fluoro-3-nitrobenzotrifluoride are dissolved in DMF, treated with 9.68 g (50.64 mmol) N-(2-Hydroxyethyl)phthalimide and 34.37 g (105.5 mmol) cesium carbonate and stirred for 30 min at 80 °C. The reaction mixture is cooled to room temperature, filtered by suction and washed with DMF. The filtrate is evaporated to dryness. The residue is taken

up in ethyl acetate, washed 3x with water and 1x with brine, dried over Na_2SO_4, filtered and concentrated to ca. 30% of its volume. The formed precipitate is filtered by suction, washed with ethyl acetate and diethylether and dried in vacuo. The mother liquor is evaporated, the solid residue digested with ethyl acetate/diethylether (8:2), filtered by suction, washed with diethylether and dried in vacuo.

From the mother liquor, additional product is obtained by chromatography (150 g silica gel, eluent: dichlormethane/MeOH - 98/2).

Yield: 10.73 g (77 %), pale yellow solid

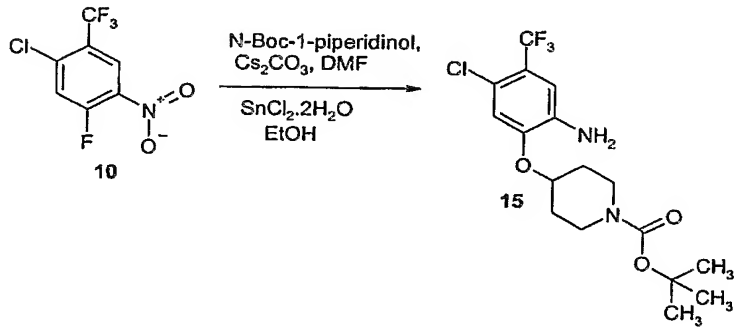
150 mg (0.36 mmol) of the nitro compounds and 404 mg (1.79 mmol) tin(II)chloride-dihydrate in THF are stirred for 1.5 h at room temperature. The reaction mixture is made alkaline with saturated $NaHCO_3$-solution. The formed precipitate is filtered off by suction over kieselguhr and washed with ethanol and ethyl acetate. The filtrate is concentrated with a Rotavapor until a water phase is obtained, which is extracted 3x with ethyl acetate. The combined organic phases are washed 1x with brine, dried over Na_2SO_4, filtered and evaporated.

Yield: 109 mg (79 %) **13**, pale yellow solid

17.7 g (39.56 mmol) **13** are suspended in 30 ml ethanol under stirring, treated with 4.81 ml (98.91 mmol) hydrazine hydrate and the reaction mixture is then heated 15h to reflux. The formed precipitate is filtered off by suction and washed with ethanol. The combined filtrates are evaporated to dryness, the residue is taken up in ethyl acetate and extracted 2x with 1N HCl-solution. The combined water phases are made alkaline with 2N NaOH-solution and extracted 3x with ethyl acetate. The combined organic phases are washed 2x with water and 1x with brine, dried over Na_2SO_4 filtered and evaporated.

Yield: 9.4 g (93 %), brown oil

8.69 g (34.1 mmol) of the accordingly obtained amine are dissolved in 50 ml dioxane, 40 ml 1N NaOH and 40 ml water by stirring at room temperature. The solution is cooled to 0 °C and at this temperature treated slowly with a solution of 8.16 g (36.8 mmol) di-tert.-butyl dicarbonate in 30 ml dioxane. The reaction mixture is slowly warmed to room temperature, stirred for 1 h. The formed precipitate is filtered off by suction, washed with water, taken up in ethyl acetate, dried over Na_2SO_4, filtered and evaporated.
Yield: 10.6 g (87 %) **14**, brown oil



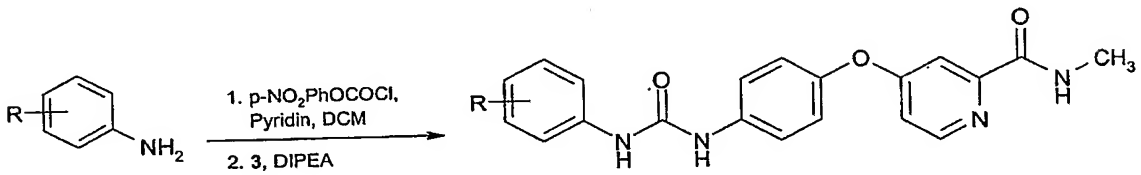
6.5 g (26.69 mmol) 5-Chloro-4-fluoro-3-nitrobenzotrifluoride, 6.45 g (32.03 mmol) N-Boc-1-piperidinol and 21.75 g (66.72 mmol) cesium carbonate are dissolved in DMF and stirred overnight at 50 °C. The reaction mixture is filtered by suction and washed with little DMF. The filtrate is evaporated. The oily residue is taken up in ethyl acetate, washed, 2x with water, dried over Na_2SO_4, filtered and evaporated. The thus obtained crude product is purified by column chromatography (700 g silica gel, eluent: ethyl acetate/petrol ether - 1/1).
Yield: 3.9 g (34 %), yellow oil

3.9 g (9.18 mmol) of the nitro compounds and 10.36 g (45.91 mmol) tin(II)chloride-dihydrate in ethanol are stirred for 2 h at room temperature. The reaction mixture is made alkaline with saturated $NaHCO_3$-solution. The formed precipitate is filtered off by suction over kieselguhr and washed with ethanol and ethyl acetate. The filtrate is concentrated with a Rotavapor until a

water phase is obtained, which is extracted 3x with ethyl acetate. The combined organic phases are washed 1x with brine, dried over Na_2SO_4, filtered and evaporated.

Yield: 3.6 g (97.5 %) **15**, brown solid

Synthesis of the ureas



16

200 µmol of the anilines **5a-k**, **8a-h**, **12a-f**, **14** and **15** are dissolved in dichloromethane together with 220 µmol p-nitrophenyl chloroformate, treated with 220 µmol pyridine at room temperature and stirred for 20-35 min. After the reaction is completed, 200 µmol **3** and 400 µmol DIPEA are added and the reaction mixture is stirred at room temperature until a full conversion is achieved (30 min - 17 h). The reaction mixture is diluted with dichloromethane, successively extracted 2x with 1N NaOH, 1x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The accordingly obtained crude product is purified according to the following variants:

Variant A: the residue is purified by column chromatography (12 g silica gel, eluent: DCM/MeOH 3% in 45-55 min).

Variant B: the oily residue is crystallised in ethyl acetate by addition of little dichloromethane and MeOH, filtered off by suction and dried.

Starting materials, reaction conditions and yields:

16a: from **5a**, 17 h, working up procedure: A, 87 %, yellow oil

16b: from **5b**, 1 h, working up procedure: A, 56 %, colourless crystals

16c: from **5c**, 1 h, working up procedure: A, 55 %, colourless crystals

16d: from **5d**, 1 h, working up procedure: A, 63 %, colourless crystals

16e: from **5e**, 1 h, working up procedure: A, 67 %, colourless crystals

16f: from **5f**, 1 h, working up procedure: A, 47 %, colourless crystals
16g: from **5g**, 30 min, working up procedure: A, 72 %, pale yellow crystals
16h: from **5h**, 45 min, working up procedure: A, 95 %, yellow oil
16i: from **5i**, 2 h, working up procedure: A, 77 %, yellow oil
16j: from **5j**, overnight, working up procedure: A, 76 %, colourless crystals
16k: from **5k**, 45 min, working up procedure: B, 59 %, colourless crystals
17a: from **8a**, 1 h, working up procedure: A, 96 %, yellow oil
17b: from **8b**, 17 h, working up procedure: A, 67.5 %, yellow oil
17c: from **8c**, 1 h, working up procedure: A, 52 %, colourless crystals
17d: from **8d**, 1 h, working up procedure: A, 55.5 %, colourless crystals
17e: from **8e**, 1 h, working up procedure: A, 54 %, colourless crystals
17f: from **8f**, 1 h, working up procedure: A, 73 %, colourless crystals
17g: from **8g**, 2 h, working up procedure: A, 71 %, colourless crystals
17h: from **8h**, 2 h, working up procedure: A, 54.5 %, colourless oil
18a: from **12a**, 30 min, working up procedure: A, 73 %, colourless crystals
18b: from **12b**, 30 min, working up procedure: A, 62 %, colourless crystals
18c: from **12c**, 1 h, working up procedure: A, 49 %, yellow crystals
18d: from **12d**, 30 min, working up procedure: A, 71 %, colourless crystals
18e: from **12e**, 1h, working up procedure: A, 66 %, beige solid
18f: from **12f**, 1 h, working up procedure: A, 65 %, yellow oil
18g: from **14**, 1 h, working up procedure: A, 75 %, yellow oil
18h: from **15**, 1 h, working up procedure: A, 65.5 %, yellow oil

Removal of the protective groups

a) BOC-protective group:

16a, 16f, 16g, 16h, 16i, 16j, 17a, 17b, 17g, 17h, 18e, 18f, 18g, 18h are treated with dichlormethane/trifluoro acetic acid - 1/1 at roomtemperature and stirred for 10 min. The reaction mixture is diluted with dichloromethane, successively extracted 2x with saturated $NaHCO_3$ solution, 2x with water, dried over Na_2SO_4, filtered and evaporated. The residue is taken up in ethyl acetate, frozen and freeze-dried overnight.

Starting materials and yields:

19a: from **16a**, 86 %, yellow solid

19b: from **16f**, 88%, yellow solid

19c: from **16g**, 99 %, colourless solid

19d: from **16h**, 94 %, colourless solid

19e: from **16i**, 77.5 %, yellow solid

19f: from **16j**, 95 %, yellow solid

19h: from **17a**, 79 %, yellow solid

19i: from **17b**, 94 %, yellow solid

19j: from **17g**, 90 %, colourless solid

19k: from **17h**, 78 %, colourless solid

19l: from **18e**, 92.5 %, yellow solid

19m: from **18f**, 92 %, yellow solid

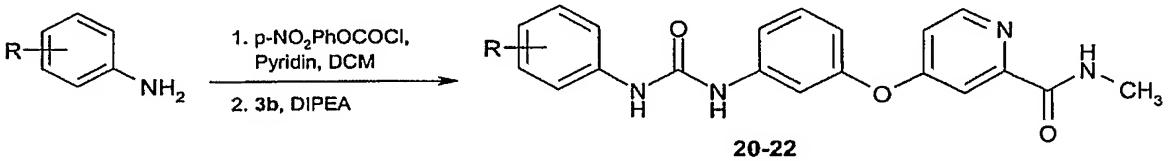
19n: from **18g**, extraction with ethylacetate, 99 %, yellow solid

19o: from **18h**, 79 %, yellow solid

b) Phthalimide-protecting group:

16k and hydrazine hydrate (1.2 equ.) in ethanol are heated to reflux for 1 h. The reaction mixture is cooled down, the formed precipitate is separated by filtration by suction and rinsed with cold ethanol. The filtrate is evaporated to dryness, the residue taken up in ethyl acetate, the formed precipitate is removed by filtration by suction and rinsed with ethylacetate. The filtrate is evaporated to dryness.

Yield : 85 %, **17g**, colourless crystals



20-22

200 µmol of the respective aniline **5a**, **5b**, **5c**, **5g**, **5h**, **5i**, **5j**, **5k**, **8a**, **8b**, **8c**, **8d**, **8h**, **12a**, **12b**, **12c**, **12d**, **12e**, **12f**, **14**, **15** are dissolved together with 200-220 µmol p-nitrophenyl chloroformate in dichloromethane, treated with 220 µmol pyridine at room temperature and stirred for 20-35 min gerührt. After the

reaction is finished, 200 µmol **3a** and 400 µmol DIPEA are added and the reaction mixture is stirred at room temperature until the full conversion is achieved. The reaction mixture is diluted with ichloromethane , extracted consecutively 1x with water, 2x with 1N NaOH, 1x with water and 1x with brine, dried over Na_2SO_4, filtered and evaporated. The accordingly obtained crude product is purified according to the following variants:

Variant A: The residue is purified by column chromatography (12 g silica gel, eluent: DCM/acetone 10%).

Variant B: The residue is purified by column chromatography (12 g silica gel, eluent: DCM/MeOH 3%).

Variant C: The residue is recrystallised from methanol, filtered by suction, rinsed with little methanol and dried.

Variant D: The residue is purified by column chromatography (12 g silica gel, eluent: Petrolether/ethylacetate – 7/3).

Variant E: The residue is recrystallised from ethylacetate, filtered by suction, rinsed with little ethyl acetate and dried.

Variant F: The residue is recrystallised from ethylacetate/petrol ether, filtered by suction, rinsed with petrol ether and dried.

Variant G: The residue is recrystallised from dichloromethane/petrol ether, filtered by suction, rinsed with little petrol ether and dried.

Variant H: The crystalline residue is digested with diethyl ether/petrol ether – 1/4 and filtered by suction. From the mother liquor, additional product is obtained by crystallization.

Starting materials, reaction conditions and yields:

20a: from **5a**, overnight, working up procedure: A, 41 %, colourless solid

20b: from **5b**, overnight, working up procedure: B, 31 %, colourless crystals

20c: from **5c**, overnight, working up procedure: B, 41.5 %, colourless crystals

20g: from **5g**, overnight, working up procedure: C, 64.5 %, colourless crystals

20h: from **5h**, overnight, working up procedure: D, 93 %, colourless crystals

20i: from **5i**, overnight, working up procedure: E, 75 %, colourless crystals

20j: from **5j**, overnight, working up procedure: B, 76 %, colourless crystals

20k: from **5k**, overnight, working up procedure: E, 82 %, colourless crystals

21a: from **8a**, overnight, working up procedure: F, 61 %, beige solid
21b: from **8b**, overnight, working up procedure: A, 34 %, orange-brown solid
21c: from **8c**, overnight, working up procedure: B, 32 %, colourless crystals
21d: from **8d**, overnight, working up procedure: B, 42 %, colourless crystals
21h: from **8h**, overnight, working up procedure: C, 39 %, beige crystals
22a: from **12a**, overnight, no working up, 81 %, yellow solid
22b: from **12b**, overnight, working up procedure: E, 30 %, colourless solid
22c: from **12c**, 3 h, working up procedure: G, 44 %, beige crystals
22d: from **12d**, 1 h, working up procedure: H, 50 %, pale yellow crystals
22e: from **12e**, overnight, working up procedure: F, 60 %, colourless solid
22f: from **12f**, overnight, working up procedure: A, 28 %, colourless solid
22g: from **14**, 4 h, working up procedure: G, 46 %, beige solid
22h: from **15**, overnight, working up procedure: F, 30 %, colourless solid

Removing the protecting groups:

a) BOC-protecting group:

20a, **20g**, **20h**, **20i**, **20j**, **21a**, **21b**, **21h**, **22e**, **22f**, **22g** and **22h** are treated with dichloromethane/trifluoro acetic acid - 1/1 at room temperature and stirred for 20-30 min. The reaction mixture is diluted with dichloromethane, washed 1x with saturated $NaHCO_3$-solution and 2x with water, dried over Na_2SO_4, filtered and evaporated. The residue is taken up in acetonitrile/water, frozen and freeze-dried overnight.

Starting materials and yields:

23a: from **20a**, 49 %, colourless solid
23b: from **20g**, 100 %, colourless crystals
23c: from **20h**, 100 %, colourless crystals
23d: from **20i**, 94 %, colourless crystals
23e: from **20j**, 95 %, colourless solid
23g: from **21a**, 72.5 %, beige solid
23h: from **21b**, 66 %, colourless solid
23i: from **21h**, 98 %, beige solid
23j: from **22e**, 94.5 %, colourless solid

23k: from **22f**, 76 %, colourless solid
23l: from **22g**, 73 %, colourless solid
23m: from **22h**, 100 %, colourless solid

b) Phthalimide-protecting group:
20k and hydrazine hydrate (1.1 equ.) in ethanol are heated 2.5 h to reflux. The reaction mixture is cooled down, the formed precipitate is separated by filtration by suction and rinsed with cold ethanol. The filtrate is evaporated to dryness, the residue taken up in ethyl acetate and extracted with 4n HCl-solution. The water phase is made alkaline with NaOH and extracted several times with ethyl acetate. The combined organic phases are washed 1x with brine, dried over Na_2SO_4, filtered and evaporated.
Yield : 40 %, 23f, colourless crystals

Retention times (Rt) as disclosed herein are, if not indicated otherwise, HPLC retention times, obtained according the following methods:

General Method:
Gradient: 5.5 min; flow rate: 2.75 ml/min from 90:10 to 0:100 H_2O/ACN
Water + TFA (0.01% by vol.); acetonitrile + TFA (0.01% by vol.)
Column: Chromolith SpeedROD RP 18e 50-4.6
Wavelength: 220 nm.

Method a:
Gradient: 5.5 min; flow rate: 2.75 ml/min from 99:1 to 0:100 H_2O/ACN
Water + TFA (0.01% by vol.); acetonitrile + TFA (0.01% by vol.)
Column: Chromolith SpeedROD RP 18e 50-4.6
Wavelength: 220 nm.

The compounds disclosed herein can preferably be produced according to the procedures described herein or in an analogous manner thereof.

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

A solution of 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

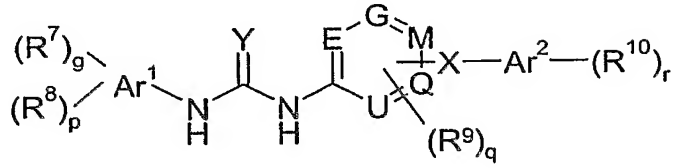
2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Claims

1. Bisarylurea derivatives of formula I



I

wherein

Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

E, G, M, Q and U are selected, independently from one another, from carbon atoms and nitrogen atoms, with the proviso that one or more of E, G, M, Q and U are carbon atoms and that X is bonded to a carbon atom,

R^7 is independently selected from a group consisting of Het, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nNR^{12}(CR^5R^6)_kNR^{11}R^{12}$,

$(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $O(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kOR^{12}$, $(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$ and $NR^{12}(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, wherein

R^5, R^6 are in each case independently from one another selected from H and A, and

n and/or k independently are 0, 1, 2, 3 or 4, preferably 1, 2, 3 or 4, and even more preferred is 2 or 3;

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nCH$=N-R^{11}, $(CH_2)_nOC(O)NR^{11}R^{12}$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{11}$, $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{13}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$,

$(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$, $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein

R^{11}, R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$, R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclus which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, which optionally is substituted by one or more substituent, selected from A, R^{13}, =O, =S and =N-R^{14},

R^{13}, R^{14} are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,

A is selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy, alkoxyalkyl and saturated heterocyclyl, preferably from the group consisting of alkyl, alkenyl, cycloalkyl, alkylenecycloalkyl, alkoxy and alkoxyalkyl,

Ar^3, Ar^4 are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, R^{13}, =O, =S, =N-R^{14}, Hal, NO_2, CN, OR^{15}, $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$,

$NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15}, $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,

R^{15}, R^{16} are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein

Ar^6 is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3,

k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,

X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein

Q is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}\text{-}O)_j$, C=O, C=S, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, C(=O)O, OC(=O), OC(=O)O, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, $OC(=O)N(R^{15})$, $N(R^{15})C(=O)O$, CH=N-O, $CH=N\text{-}NR^{15}$, $OC(O)NR^{15}$, $NR^{15}C(O)O$, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and

j is 1, 2, 3, 4, 5, or 6,

Y is selected from O, S, NR^{21}, $C(R^{22})\text{-}NO_2$, $C(R^{22})$-CN and $C(CN)_2$, wherein

R^{21} is independently selected from the meanings given for R^{13}, R^{14} and

R^{22} is independently selected from the meanings given for R^{11}, R^{12},

g is 1, 2 or 3, preferably 1 or 2,

p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

Hal is independently selected from a group consisting of F, Cl, Br and I;

and the pharmaceutically acceptable derivatives, salts and solvates thereof.

2. Bisarylurea derivatives according to claim 1,

wherein

Ar^1, Ar^2 are selected independently from one another from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

R^7 is independently selected from a group consisting ofHet, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_nNR^{12}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_nO(CR^5R^6)_kOR^{11}$, $NR^{11}(CR^5R^6)_nO(CR^5R^6)_kOR^{12}$, $O(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$ and $NR^{12}(CR^5R^6)_nNR^{11}(CR^5R^6)_kOR^{12}$, wherein

R^5, R^6 are in each case independently from one another selected from H and A, and

n and/or k independently are 0, 1, 2, 3 or 4, preferably 1, 2, 3 or 4, and even more preferred are 2 or 3;

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal, $CH(Hal)_2$, $C(Hal)_3$, NO_2, $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kOR^{11}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $(CH_2)_nN(R^{11})C(R^{13})HCOR^{11}$, $(CH_2)_nN(COOR^{13})COOR^{14}$,

$(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$, wherein

n and/or k independently are 0, 1, 2, 3 or 4, preferably 0, 1, 2 or 3, and even more preferred are 0 or 2;

X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h$-Q-$(CHR^{12})_i$, wherein

Q is selected from a group consisting of O, S, N-R^{15}, $(CHal_2)_j$, $(O\text{-}CHR^{18})_j$, $(CHR^{18}\text{-}O)_j$, $CR^{18}=CR^{19}$, $(O\text{-}CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}\text{-}O)_j$, C=O, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, $CH=N\text{-}NR^{15}$, S=O, SO_2, SO_2NR^{15} and $NR^{15}SO_2$, wherein

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

g is 1 or 2, preferably 1,

p is 1, 2 or 3, preferably 1 or 2, and

r is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the pharmaceutically acceptable derivatives, solvates, salts and stereoisomers thereof

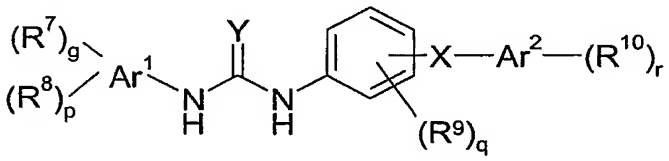
3. Bisarylurea derivatives according to claim 1 or 2,

wherein

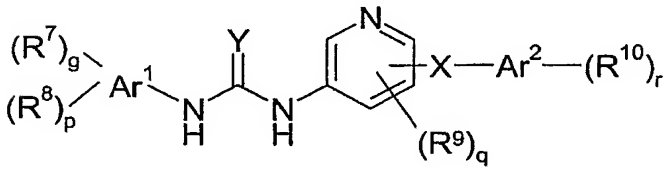
R^7 is independently selected from a group consisting of Het, OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $(CR^5R^6)_kNR^{11}R^{12}$, $(CR^5R^6)_kOR^{13}$, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kR^{13}$, $NR^{11}(CR^5R^6)_kR^{13}$, $O(CR^5R^6)_kOR^{13}$, $NR^{11}(CR^5R^6)_kOR^{13}$, and more preferably from OHet, $N(R^{11})$Het, $(CR^5R^6)_k$Het, $O(CR^5R^6)_k$Het, $N(R^{11})(CR^5R^6)_k$Het, $O(CR^5R^6)_kNR^{11}R^{12}$, $NR^{11}(CR^5R^6)_kNR^{11}R^{12}$, $O(CR^5R^6)_kOR^{13}$ and $NR^{11}(CR^5R^6)_kOR^{13}$, wherein

n and k are independently from one another 1, 2, 3 or 4.

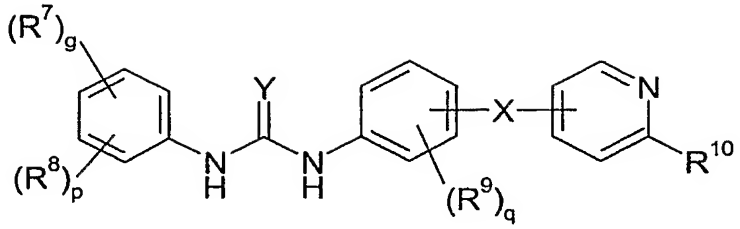
4. Bisarylurea derivative according to one of the claims 1 to 3, selected from the compounds of formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, IL, Im, In, Io, Ip, Iq, Ir, Is, It, Iu, Iv and Iw,



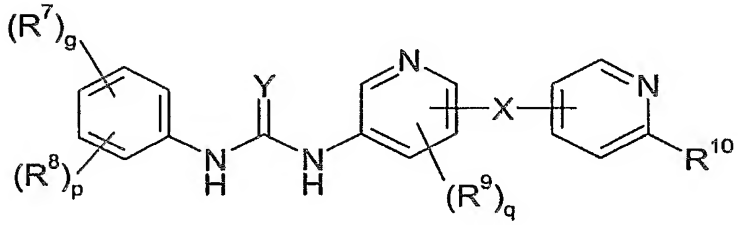
Ia



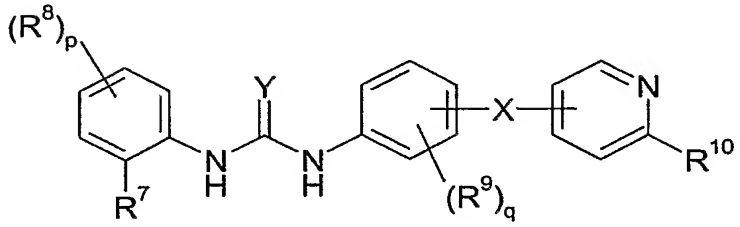
Ib



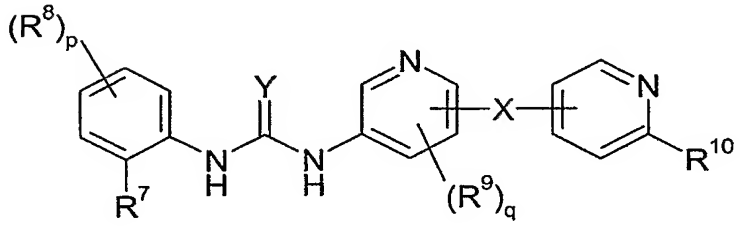
Ic



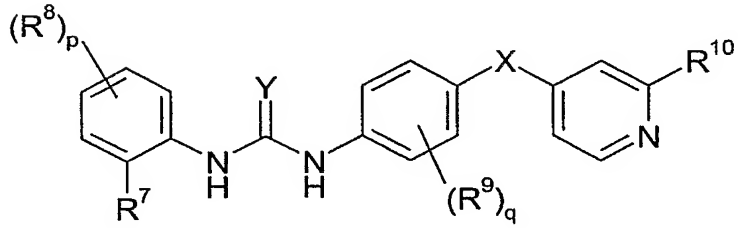
Id



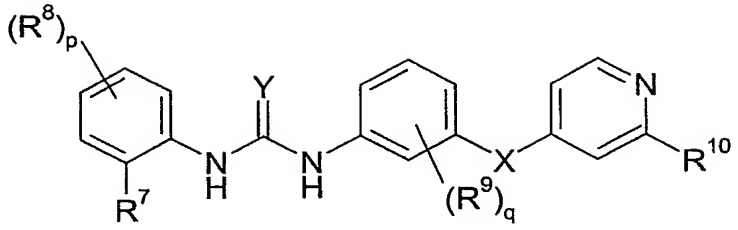
Ie



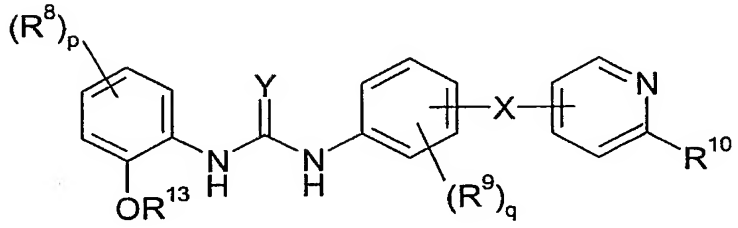
If



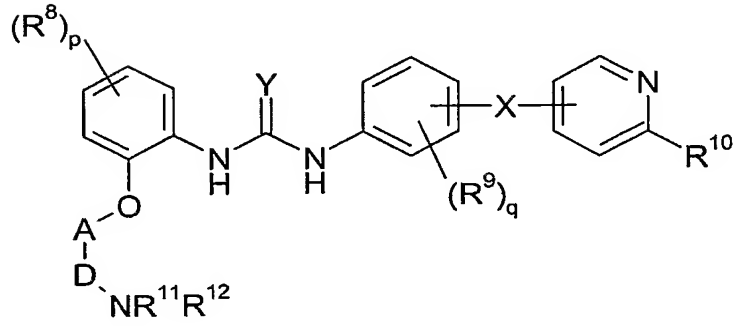
Ig



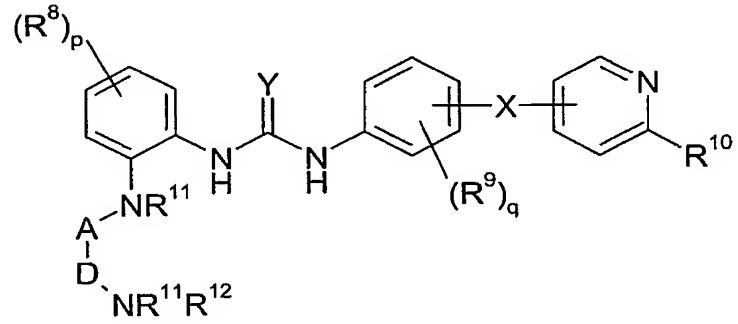
Ih



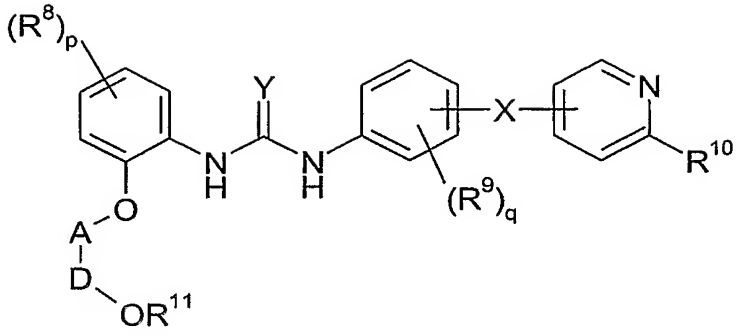
Ii



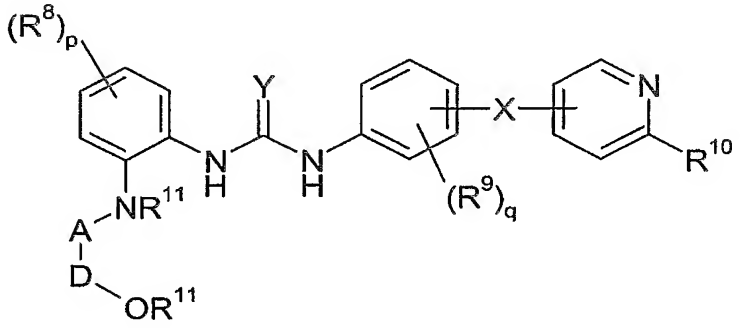
Ij



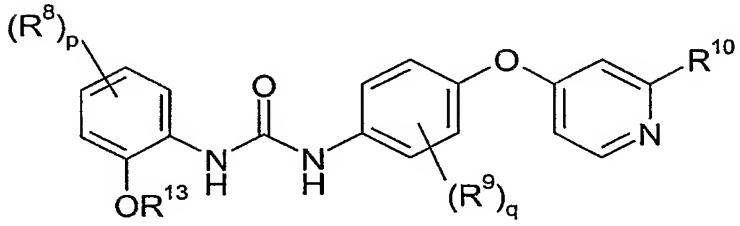
Ik



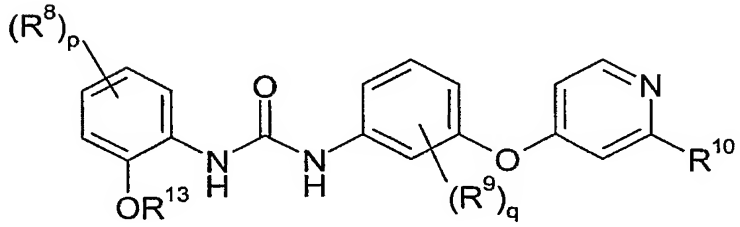
IL



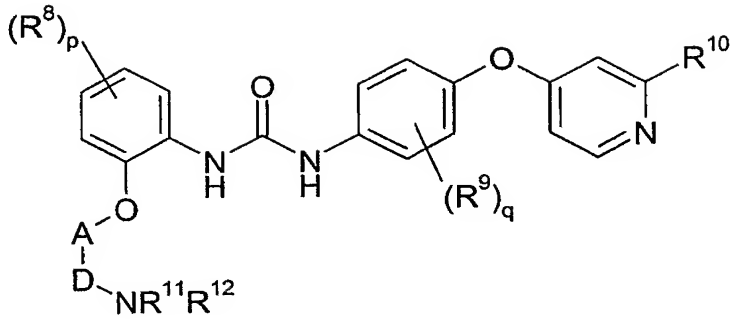
Im



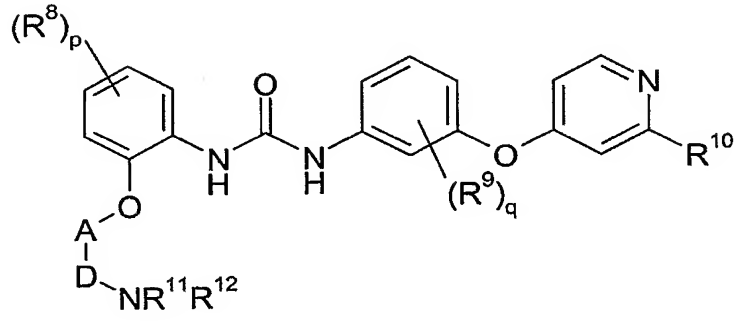
In



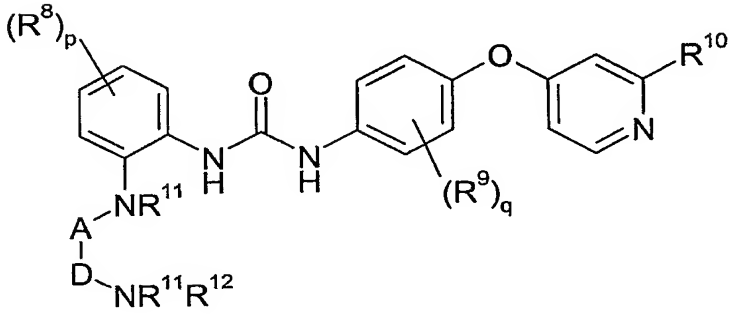
Io



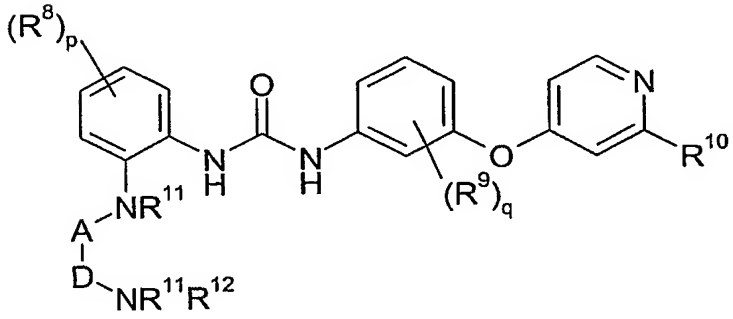
Ip



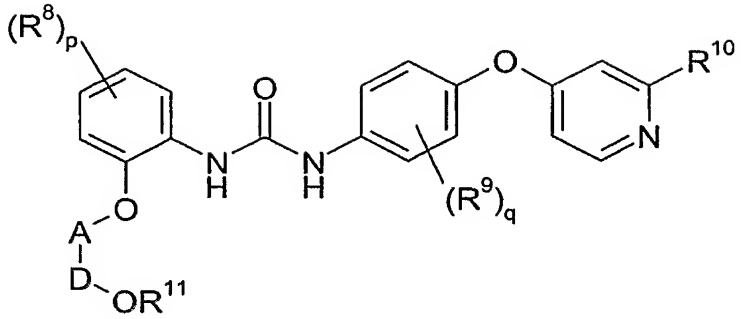
Iq



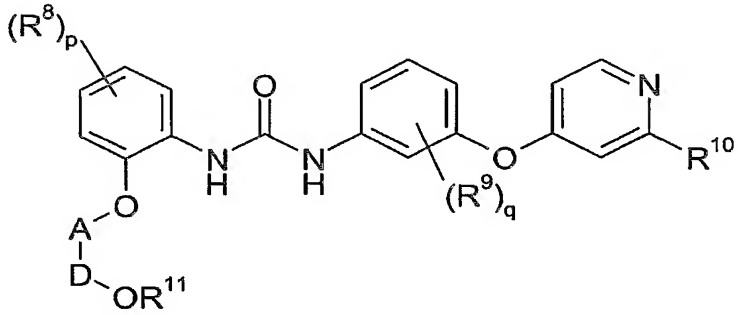
Ir



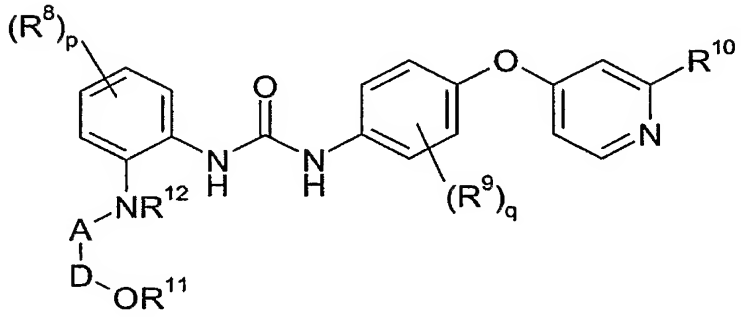
Is



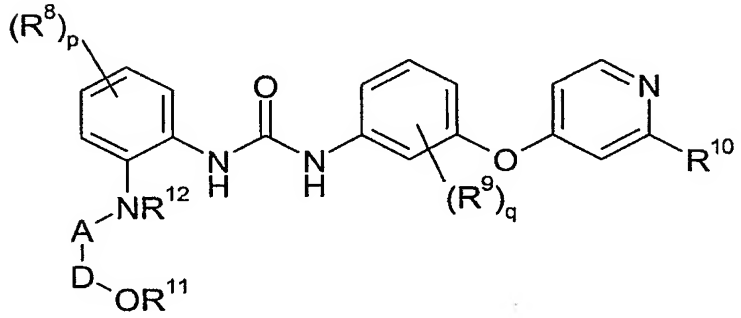
It



Iu



Iv



Iw

wherein R^7, R^8, R^{11}, R^{12}, R^{13}, Y, X, R^9, A, D, g, p and q are as defined in one of the claims 1 to 3, R^{10} is H or as defined in one of the claims 1 to

3; and A and D are CR^5R^6, wherein R^5 and R^6 are as defined in claim 1, and the pharmaceutically acceptable derivatives, salts and solvates thereof.

5. Bisarylurea derivative according to claim one of the claims 1 to 4, selected from 4-(4-{3-[4-Chloro-5-methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[Chloro-(2-methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[(2-Methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide;
4-(4-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[Chloro-(2-diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[Chloro-(2-morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide and
4-(4-{3-[Chloro-(2-pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide;
4-(4-{3-[Chloro-(piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Amino-ethoxy)-chloro-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(4-{3-[2-(2-Amino-ethoxy)-4-chloro-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Amino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[Chloro-(2-piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[4-Chloro-2-(2-dimethylamino-ethoxy)-5-methyl-phenyl]-ureido}-

phenoxy)-pyridine-2-carboxylicacid methylamide
4-(4-{3-[4-Chloro-2-(2-diethylamino-ethoxy)-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylicacid methylamide
4-(4-{3-[4-Chloro-5-methyl-2-(2-morpholin-4-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[4-Chloro-5-methyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Morpholin-4-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Diethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(4-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[4-Chloro-5-methyl-2-(2-piperazin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[4-Chloro-5-methyl-2-(piperidin-4-yloxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(4-{3-[(2-Piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(Piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(Pyrrolidin-2-ylmethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(4-{3-[(2-Amino-2-methyl-propoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(2-Amino-ethoxy)-chloro-trifluoromethyl-phenyl]-ureido}-

phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(3-{3-[(2-Methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(4-{3-[(2-Isopropylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[4-Chloro-5-methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-methylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(2-piperazin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[Chloro-(piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[2-(2-Amino-ethoxy)-4-chloro-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(2-Dimethylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[4-Chloro-2-(2-dimethylamino-ethoxy)-5-methyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylicacid methylamide
4-(3-{3-[4-Chloro-5-methyl-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(2-Pyrrolidin-1-yl-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(Piperidin-4-yloxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[4-Chloro-5-methyl-2-(piperidin-4-yloxy)-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acidmethylamide
4-(3-{3-[(2-Amino-2-methyl-propoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(2-Isopropylamino-ethoxy)-trifluoromethyl-phenyl]-ureido}-

phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(Pyrrolidin-2-ylmethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
4-(3-{3-[(2-Amino-ethoxy)-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyridine-2-carboxylic acid methylamide
and the pharmaceutically acceptable derivatives, salts and solvates thereof.

6. Bisarylurea derivative according to one of the claims 1 to 5 as a medicament.

7. Bisarylurea derivative according to one of the claims 1 to 5 as a kinase inhibitor.

8. Bisarylurea derivative according to claim 7, characterized in that the kinases are selected from raf-kinases.

9. Pharmaceutical composition, characterised in that it contains one or more compounds according to one of the claims 1 to 5.

10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.

11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a pharmaceutical

composition that is suitable as dosageform for application and/or administration to a patient.

12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.

13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.

14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.

15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.

16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.

17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.

18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.

19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the disorders are selected from the group consisting of psioarsis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, begnin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.

20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancar, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.

21. Use according to one of the claims 13 to 18, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.

22. Use according to one of the claims 13 to 16, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.

23. Use of a compound according to one of the claims 1 to 5 as a raf-kinase inhibitor.

24. Use according to claim 23, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf1.

25. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.

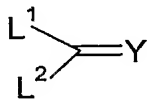
26. Method according to claim 25, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are administered as a pharmaceutical composition according to claim 9 or 10.

27. Method for the treatment and/or prophylaxis of disorders according to claim 26, characterised in that the disorders are as defined in one of the claims 15 to 22.

28. Method for the treatment according to claim 27, characterised in that the disorder is cancerous cell growth mediated by raf-kinase.

29. Method for producing compounds of formula I, characterised in that

a) a compound of formula II,

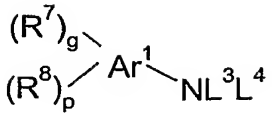


wherein

L^1 and L^2 either independently from one another represent a leaving group, or together represent a leaving group, and Y is as defined above/below,

is reacted with

b) a compound of formula III



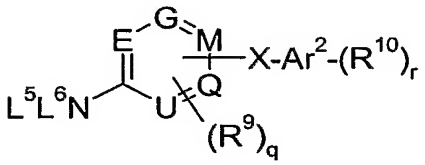
III

wherein

L3 and L4 are independently from one another H or a metal ion, and wherein R7, R8, g, p and Ar1 are as defined in claim 1,

and

c) a compound of formula IV,



IV

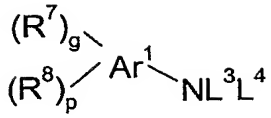
wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, G, M, Q, U, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 1,

and optionally

d) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

30. Compound of formula III,

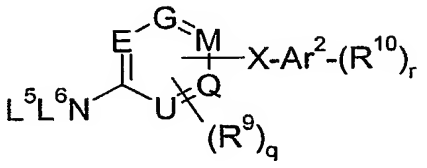


III

wherein

L^3 and L^4 are independently from one another H or a metal ion, and wherein R^7, R^8, g, p and Ar^1 are as defined in claim 1.

31. Compound of formula IV,



IV

wherein

L^5 and L^6 are independently from one another H or a metal ion, and E, G, M, Q, U, R^9, q, X, Ar^2, R^{10} and r are as defined in claim 1.

Abstract

The present invention relates to bisarylurea derivatives of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.